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(54) Title: PHARMACEUTICAL COMPOSITIONS AND METHODS COMPRISING COMBINATIONS OF 2-ALKYLIDENE-19-NOR-VITAMIN D DERIVATIVES AND AN ESTROGEN AGONIST/ANTAGONIST

(57) Abstract: The present invention relates to pharmaceutical compositions and methods of treatment comprising administering to a patient in need thereof a combination of a 2-alkylidene-19-nor-vitamin D derivative and an estrogen agonist/antagonist or a pharmaceutically acceptable salt or prodrug thereof. Particularly, the present invention relates to pharmaceutical compositions and methods of treatment comprising administering to a patient in need thereof 2-methylene-19-nor-20(S)la,25-dihydroxyvitamin D_3 and (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol, or a pharmaceutically acceptable salt or prodrug thereof.

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PHARMACEUTICAL COMPOSITIONS AND METHODS COMPRISING COMBINATIONS OF 2-ALKYLIDENE-19-NOR-VITAMIN D DERIVATIVES AND AN ESTROGEN AGONIST/ANTAGONIST

Field of the Invention

The present invention relates to pharmaceutical compositions and methods of treatment comprising administering to a patient in need thereof a combination of a 2-alkylidene-19-nor-vitamin D derivative and an estrogen agonist/antagonist or a pharmaceutically acceptable salt or prodrug thereof. Particularly, the present invention relates to pharmaceutical compositions and methods of treatment comprising administering to a patient in need thereof 2-methylene-19-nor-20(S)-1α,25-dihydroxyvitamin D_3 and (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol, or a pharmaceutically acceptable salt or prodrug thereof.

Background of the Invention

Vitamin D is a general term that refers to a group of steroid molecules. The active form of vitamin D, which is called 1,25-dihydroxyvitamin D_3 (1,25-dihydroxycholecalciferol), is biosynthesized in humans by the conversion of 7-dehydrocholesterol to vitamin D_3 (cholecalciferol). This conversion takes place in the skin and requires UV radiation, which is typically from sunlight. Vitamin D_3 is then metabolized in the liver to 25-hydroxyvitamin D_3 (25-hydroxycholecalciferol), which is then further metabolized in the kidneys to the active form of vitamin D, 1,25-dihydroxvitamin D_3. 1,25-dihydroxyvitamin D_3 is then distributed throughout the body where it binds to intracellular vitamin D receptors.

The active form of vitamin D is a hormone that is known to be involved in mineral metabolism and bone growth and facilitates intestinal absorption of calcium.

Vitamin D analogs are disclosed in U.S. Patent No. 5,843,928, issued December 1, 1998. The compounds disclosed are 2-alkylidene-19-nor-vitamin D derivatives and are characterized by low intestinal calcium transport activity and high bone calcium mobilization activity when compared to 1,25-dihydroxyvitamin D_3.

The present invention provides for methods of treatment using a combination of a 2-alkylidene-19-nor-vitamin D derivative, and particularly the compound 2-methylene-19-nor-20(S)-1α,25-dihydroxyvitamin D_3, (also known as 2MD), and an estrogen agonist/antagonist or a pharmaceutically acceptable salt or prodrug thereof.

Summary of the Invention

The present invention provides pharmaceutical compositions comprising the compound 2-methylene-19-nor-20(S)-1α,25-dihydroxyvitamin D_3 and an estrogen agonist/antagonist or a pharmaceutically acceptable salt or prodrug thereof. The present invention also provides methods of treating senile osteoporosis, postmenopausal osteoporosis, bone fractures, bone grafts, breast cancer, prostate cancer, obesity, osteopenia, male osteoporosis, frailty, muscle damage or sarcopenia, the methods comprising administering to a patient in need thereof a therapeutically effective amount of 2-methylene-19-nor-20(S)-1α,25-dihydroxyvitamin D_3 and an estrogen agonist/antagonist or a pharmaceutically acceptable salt or prodrug thereof.

Detailed Description of the Invention

The present invention relates to pharmaceutical compositions and methods of treating metabolic bone disease, senile osteoporosis, postmenopausal osteoporosis, steroid induced osteoporosis, low bone turnover osteoporosis, osteomalacia, renal osteodystrophy, psoriasis, multiple sclerosis, diabetes mellitus, host versus graft rejection, transplant rejection, rheumatoid arthritis, asthma, bone fractures, bone grafts, acne, alopecia, dry skin, insufficient skin firmness, insufficient sebum secretion, wrinkles, hypertension, leukemia, colon cancer, breast cancer, prostate cancer, obesity, osteopenia, male osteoporosis, hypogonadism, andropause, frailty, muscle damage, sarcopenia, osteosarcoma, hypocalcemic tetany, hypoparathyroidism, rickets, vitamin D deficiency, anorexia, low bone mass resulting from aggressive athletic behavior, and for enhancement of peak bone mass in adolescence and prevention of second hip fracture using a combination of a 2-alkylidene-19-nor-vitamin D derivative and an estrogen agonist/antagonist.

In a preferred embodiment, the present invention relates to a method of treating metabolic bone disease, senile osteoporosis, postmenopausal osteoporosis, steroid induced osteoporosis, low bone turnover osteoporosis, osteomalacia, renal osteodystrophy, psoriasis, multiple sclerosis, diabetes mellitus, host versus graft rejection, transplant rejection, rheumatoid arthritis, asthma, bone fractures, bone grafts, acne, alopecia, dry skin, insufficient skin firmness, insufficient sebum secretion, wrinkles, hypertension, leukemia, colon cancer, breast cancer, prostate

cancer, obesity, osteopenia, male osteoporosis, hypogonadism, andropause, frailty, muscle damage, sarcopenia, osteosarcoma, hypocalcemic tetany, hypoparathyroidism, rickets, vitamin D deficiency, anorexia, low bone mass resulting from aggressive athletic behavior, and for enhancement of peak bone mass in adolescence and prevention of second hip fracture using 2-methylene-19-nor-20(S)-1α,25-dihydroxyvitamin D_3 and an estrogen agonist/antagonist or a pharmaceutically acceptable salt or prodrug thereof.

In a preferred embodiment, the methods of treatment using the combination are senile osteoporosis, postmenopausal osteoporosis, bone fractures, bone grafts, breast cancer, prostate cancer, obesity, osteopenia, male osteoporosis, frailty, muscle damage and sarcopenia.

Osteopenia is a thinning of the bones, but less than is seen with osteoporosis and is the stage before true osteoporosis. The World Health Organization has developed diagnostic categories based on bone mass density (BMD) to indicate if a person has normal bones, has osteopenia or has osteoporosis. Normal bone density is within one standard deviation (+1 or -1) of the young adult mean bone density. Osteopenia (low bone mass) is defined as a bone density 1 to 2.5 standard deviations below the young adult mean (-1 to –2.5), and osteoporosis is defined as a bone density which is 2.5 standard deviations or more below the young adult mean (>-2.5).

Hypogonadism is generally defined as inadequate gonadal function, as manifested by deficiencies in gametogenesis and/or the secretion of gonadal hormones, which can result in retardation of puberty and/or reproductive insufficiency. There are three main types of hypogonadism: 1) primary hypogonadism; 2) secondary hypogonadism; and 3) resistance hypogonadism. In primary hypogonadism damage to the Leydig cells impairs androgen production. In secondary hypogonadism disorder of the hypothalamus or pituitary impairs gonadotropin secretion and in resistance hypogonadism, the body response to androgen is inadequate.

Rickets is a childhood disorder involving softening and weakening of the bones, primarily caused by lack of vitamin D, calcium, and/or phosphate.

Anorexia is a disease that has the following characterisitcs: refusal to maintain body weight at or above a minimally normal weight for age and height (e.g., weight loss leading to maintenance of body weight less than 85% of that expected; or failure

to make expected weight gain during period of growth, leading to body weight less than 85% of that expected);intense fear of gaining weight or becoming fat, even though underweight; and disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight. The compounds and combinations of the present invention can be used to treat anorexia and can be used to treat bone loss associated with anorexia.

Another condition that can be treated using the compounds and combinations of the present invention is bone loss associated with aggressive athletic behavior, particularly in women. Aggressive participation in exercise, athletics or sports can result in bone loss, which is usually accompanied in women by ammenorhea. Men who also exhibit aggressive athletic behavior also exhibit bone loss.

Andropause (also called male menopause or viropause) is a natural occurrence in men that typically happens between the age of forty and fifty-five. Andropause is a decline in the level of the hormone testosterone. As testosterone levels decline, and men enter andropause, various changes or conditions may be observed including decreased energy and strength, increased body fat, osteoporosis, depression, decreased mental acuity, inability to maintain muscle, cardiovascular disease, atherosclerosis, decreased libido, decreased strength of orgasms, erectile dysfunction, increased irritability, and aching and stiff joints, particularly in the hands and feet. In addition, males undergoing or having undergone andropause can have gynecomastia, serum lipid disorders, including hypercholesterolemia, reduced vascular reactivity, hypogonadism, and benign prostatic hyperplasia.

Frailty is characterized by the progressive and relentless loss of skeletal muscle mass resulting in a high risk of injury from fall, difficulty in recovery from illness, prolongation of hospitalization, and long-term disability requiring assistance in daily living. The reduction of muscle mass, physical strength and physical performance typically leads to diminished quality of life, loss of independence, and mortality. Frailty is normally associated with aging, but may also result when muscle loss and reduced strength occur due to other factors, such as disease-induced cachexia, immobilization, or drug-induced sarcopenia. Another term that has been used to denote frailty is sarcopenia, which is a generic term for the loss of skeletal muscle mass, or quality. Examples of skeletal muscle properties that contribute to its

overall quality include contractility, fiber size and type, fatiguability, hormone responsiveness, glucose uptake/metabolism, and capillary density. Loss of muscle quality, even in the absence of loss of muscle mass, can result in loss of physical strength and impaired physical performance.

The term 'muscle damage' as used herein is damage to any muscle tissue. Muscle damage can result from physical trauma to the muscle tissue as the result of accidents, athletic injuries, endocrine disorders, disease, wounds or surgical procedures. The methods of the present invention are useful for treating muscle damage by facilitating muscle damage repair.

Osteoporosis in the elderly woman is determined by the amount of peak bone mass gained in adolescence leading to adulthood, the premenopausal maintenance of such peak bone mass, and the rate of postmenopausal bone mass loss. Determinants of peak bone mass include genetic, nutritional, weight loading (exercise), and environmental factors. Enhancement of peak bone mass in adolescence is therefore desirable in order to maximize the skeletal mass in order to prevent the development of osteoporosis later in life. Likewise, enhancement of peak bone mass in adolescence for males is also desirable.

Hip fracture has a significant impact on medical resources and patient morbidity and mortality. Few patients admitted with a hip fracture are considered for prophylactic measures aimed at the reduction of further fracture risk. Currently, 10-13% of patients will later sustain a second hip fracture. Of patients who suffered a second hip fracture, fewer patients maintained their ability to walk independently after the second fracture than did so after the first (53 and 91% respectively, $P<0.0005$). Pearse E.O. et al., Injury, 2003, *34(7)*, 518-521. Following second hip fracture, patients' level of mobility determined their future social independence. Older patients and those with a history of multiple falls had a shorter time interval between fractures. Second hip fracture has a significant further impact on patients' mobility and social independence. It is therefore desirable to have new methods for the prevention of second hip fracture.

Osteosarcoma is a relatively common, highly malignant primary bone tumor that has a tendency to metastasize to the lungs. Osteosarcoma is most common in persons 10 to 20, though it can occur at any age. About half of all osteosarcomas are located in the region of the knee but it can be found in any bone. Pain and a mass are the usual symptoms of osteosarcoma. Typical treatment for osteosarcoma

is chemotherapy in combination with surgery. Either preoperative or postoperative chemotherapy with agents such as methotrexate, doxorubicin, cisplatin or carboplatin can be used to treat the osteosarcoma.

Hypoparathyroidism is a tendency to hypocalcemia, often associated with chronic tetany resulting from hormone deficiency, characterized by low serum calcium and high serum phosphorus levels. Hypoparathyroidism usually follows accidental removal of or damage to several parathyroid glands during thyroidectomy. Transient hypoparathyroidism is common following subtotal thyroidectomy and occurs permanently in less than three percent of expertly performed thyroidectomies.

Hypocalcemic tetany is a form of tetany resulting from hypocalcemia. Hypocalcemia is characterized by a decrease in total plasma calcium concentration below 8.8 mg/dL (milligrams/deciliter) in the presence of normal plasma protein concentration. Tetany may be overt with spontaneous symptoms or latent. Tetany, when overt, is characterized by sensory symptoms such as paresthesias of the lips, tongue, fingers and feet; carpopedal spasm, which may be prolonged and painful; generalized muscle aching; and spasm of facial musculature. Latent tetany requires provocative tests to elicit and generally occurs at less severely decreased plasma calcium concentrations, such as 7 to 8 mg/dL. Hypocalcemic tetany is also observed in veterinary practice in animals. For example, hypocalcemic tetany in horses is a rare condition associated with acute depletion of serum ionized calcium and sometimes with alterations in serum concentrations of magnesium and phosphate. It occurs after prolonged physical exertion or transport (transport tetany) and in lactating mares (lactation tetany). Signs are variable and relate to neuromuscular hyperirritability.

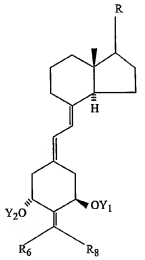
The present invention is also concerned with pharmaceutical compositions for treating metabolic bone disease, senile osteoporosis, postmenopausal osteoporosis, steroid induced osteoporosis, low bone turnover osteoporosis, osteomalacia, renal osteodystrophy, psoriasis, multiple sclerosis, diabetes mellitus, host versus graft rejection, transplant rejection, rheumatoid arthritis, asthma, bone fractures, bone grafts, acne, alopecia, dry skin, insufficient skin firmness, insufficient sebum secretion, wrinkles, hypertension, leukemia, colon cancer, breast cancer, prostate cancer, obesity, osteopenia, male osteoporosis, hypogonadism, andropause, frailty, muscle damage, sarcopenia, osteosarcoma, hypocalcemic tetany, hypoparathyroidism, rickets, vitamin D deficiency, anorexia, low bone mass resulting

from aggressive athletic behavior, and for enhancement of peak bone mass in adolescence and prevention of second hip fracture comprising a 2-alkylidene-19-nor-vitamin D derivative, such as a compound of Formula I, and an estrogen agonist/antagonist or a pharmaceutically acceptable salt or prodrug thereof and a carrier, solvent, diluent and the like.

In one embodiment, the combinations of this invention comprise a therapeutically effective amount of a first compound, said first compound being an 2-alkylidene-19-nor-vitamin D derivative, such as a compound of Formula I; and a therapeutically effective amount of a second compound, the second compound being an estrogen agonist/antagonist or a pharmaceutically acceptable salt or prodrug thereof.

A particularly preferred combination is a combination of 2-methylene-19-nor-20(S)-1α,25-dihydroxyvitamin D_3 and (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol, particularly the D-tartrate salt.

2-Alkylidene-19-nor-vitamin D derivatives that can be used in the present invention are disclosed U.S. Patent No. 5,843,928, which derivatives are characterized by the general formula I shown below:



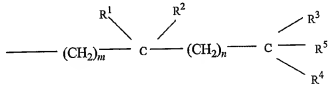
I

where Y_1 and Y_2, which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, R_6 and R_8, which

may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl and fluoroalkyl, or, when taken together represent the group $-(CH_2)_x-$ where X is an integer from 2 to 5, and where the group R represents any of the typical side chains known for vitamin D type compounds.

More specifically R can represent a saturated or unsaturated hydrocarbon radical of 1 to 35 carbons, that may be straight-chain, branched or cyclic and that may contain one or more additional substituents, such as hydroxy- or protected-hydroxy groups, fluoro, carbonyl, ester, epoxy, amino or other heteroatomic groups. Preferred side chains of this type are represented by the structure below:

where the stereochemical center (corresponding to C-20 in steroid numbering) may have the R or S configuration (i.e., either the natural configuration about carbon 20 or the 20-epi configuration), and where Z is selected from Y, $-OY$, $-CH_2OY$, $-C{\equiv}CY$ and $-CH{=}CHY$, where the double bond may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, $-COR^5$ and a radical of the structure:



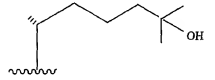
where m and n, independently, represent the integers from 0 to 5, where R^1 is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C_{1-5}-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R^2, R^3 and R^4, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C_{1-5} alkyl, which may be straight-chain or branched, and

optionally, bear a hydroxy or protected-hydroxy substituent, and where R^1 and R^2, taken together, represent an oxo group, or an alkylidene group, $=CR^2R^3$, or the group $-(CH_2)_p-$, where p is an integer from 2 to 5, and where R^3 and R^4, taken together, represent an oxo group, or the group $-(CH_2)_q-$, where q is an integer from 2 to 5, and where R^5 represent hydrogen, hydroxy, protected hydroxy, or C_{1-5} alkyl and wherein any of the CH-groups at positions 20, 22 or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups $-CH(CH_3)-$, $-CH(R^3)-$, or $-CH(R^2)-$ at positions 20, 22 and 23, respectively, may be replaced by an oxygen or sulfur atom.

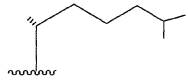
The wavy line to the methyl substituent at C-20 indicates that carbon 20 may have either the R or S configuration.

Specific important examples of side chains with natural 20R-configuration are the structures represented by formulas (a), (b), (c), (d) and (e) below, i.e., the side chain as it occurs in 25-hydroxyvitamin D_3 (a); vitamin D_3 (b); 25-hydroxyvitamin D_2 (c); vitamin D_2 (d); and the C-24 epimer of 25-hydroxyvitamin D_2 (e);

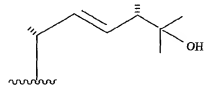
(a)



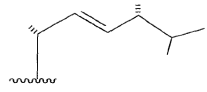
(b)



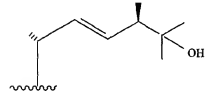
(c)



(d)



(e)



As used herein, the term "hydroxy-protecting group" signifies any group commonly used for the temporary protection of hydroxy functions, such as for example, alkoxycarbonyl, acyl, alkylsilyl or alkylarylsilyl groups (hereinafter referred to simply as "silyl" groups), and alkoxyalkyl groups. Alkoxycarbonyl protecting groups are alkyl-O-CO- groupings such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, benzyloxycarbonyl or allyloxycarbonyl. The term "acyl" signifies an alkanoyl group of 1 to 6 carbons, in all of its isomeric forms, or a carboxyalkanoyl group of 1 to 6 carbons, such as an oxalyl, malonyl, succinyl, or glutaryl group, or an aromatic acyl group such as benzoyl, or a halo, nitro or alkyl substituted benzoyl group. The word "alkyl" as used in the description or the claims, denotes a straight-chain or branched alkyl radical of 1 to 10 carbons, in all its isomeric forms. Alkoxyalkyl protecting groups are groupings such as methoxymethyl, ethoxymethyl, methoxyethoxymethyl, or tetrahydrofuranyl and tetrahydropyranyl. Preferred silyl-protecting groups are trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, dibutylmethylsilyl, diphenylmethylsilyl, phenyldimethylsilyl, diphenyl-t-butylsilyl and analogous alkylated silyl radicals. The term "aryl" specifies a phenyl-, or any alkyl-, nitro- or halo-substituted phenyl group.

A "protected hydroxy" group is a hydroxy group derivatized or protected by any of the above groups commonly used for the temporary or permanent protection of hydroxy functions, e.g., the silyl, alkoxyalkyl, acyl or alkoxycarbonyl groups, as

previously defined. The terms "hydroxyalkyl", "deuteroalkyl" and "fluoroalkyl" refer to any alkyl radical substituted by one or more hydroxy, deuterium or fluoro groups respectively.

It should be noted in this description that the term "24-homo" refers to the addition of one methylene group and the term "24-dihomo" refers to the addition of two methylene groups at the carbon 24 position in the side chain. Likewise, the term "trihomo" refers to the addition of three methylene groups. Also, the term "26,27-dimethyl" refers to the addition of a methyl group at the carbon 26 and 27 positions so that for example R^3 and R^4 are ethyl groups. Likewise, the term "26,27-diethyl" refers to the addition of an ethyl group at the 26 and 27 positions so that R^3 and R^4 are propyl groups.

In the following lists of compounds, the particular alkylidene substituent attached at the carbon 2 position should be added to the nomenclature. For example, if a methylene group is the alkylidene substituent, the term "2-methylene" should precede each of the named compounds. If an ethylene group is the alkylidene substituent, the term "2-ethylene" should precede each of the named compounds, and so on. In addition, if the methyl group attached at the carbon 20 position is in its epi or unnatural configuration, the term "20(S)" or "20-epi" should be included in each of the following named compounds. The named compounds could also be of the vitamin D_2 type if desired.

Specific and preferred examples of the 2-alkylidene-compounds of structure I when the side chain is unsaturated are:

19-nor-24-homo-1,25-dihydroxy-22-dehydrovitamin D_3;
19-nor-24-dihomo-1,25-dihydroxy-22-dehydrovitamin D_3;
19-nor-24-trihomo-1,25-dihydroxy-22-dehydrovitamin D_3;
19-nor-26,27-dimethyl-24-homo-1,25-dihydroxy-22-dehydrovitamin D_3;
19-nor-26,27-dimethyl-24-dihomo-1,25-dihydroxy-22-dehydrovitamin D_3;
19-nor-26,27-dimethyl-24-trihomo-1,25-dihydroxy-22-dehydrovitamin D_3;
19-nor-26,27-diethyl-24-homo-1,25-dihydroxy-22-dehydrovitamin D_3;
19-nor-26,27-diethyl-24-dihomo-1,25-dihydroxy-22-dehydrovitamin D_3;
19-nor-26,27-diethyl,24-trihomo-1,25-dihydroxy-22-dehydrovitamin D_3;
19-nor-26,27-dipropyl-24-homo-1,25-dihydroxy-22-dehydrovitamin D_3;
19-nor-26,27-dipropyl-24-dihomo-1,25-dihydroxy-22-dehydrovitamin D_3; and
19-nor-26,27-dipropyl-24-trihomo-1,25-dihydroxy-22-dehydrovitamin D_3.

Specific and preferred examples of the 2-alkylidene-compounds of structure I when the side chain is saturated are:

19-nor-24-homo-1,25-dihydroxyvitamin D_3;

19-nor-24-dihomo-1,25-dihydroxyvitamin D_3;

19-nor-24-trihomo-1,25-dihydroxyvitamin D_3;

19-nor-26,26-dimethyl-24-homo-1,25-dihydroxyvitamin D_3;

19-nor-26,27-dimethyl-24-dihomo-1,25-dihydroxyvitamin D_3;

19-nor-26,27-dimethyl-24-trihomo-1,25-dihydroxyvitamin D_3;

19-nor-26,27-diethyl-24-homo-1,25-dihydroxyvitamin D_3;

19-nor-26,27-diethyl-24-dihomo-1,25-dihydroxyvitamin D_3;

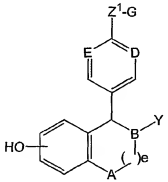
19-nor-26,27-diethyl-24-trihomo-1,25-dihydroxyvitamin D_3;

19-nor-26,27-dipropyl-24-homo-1,25-dihydroxyvitamin D_3;

19-nor-26,27-dipropyl-24-dihomo-1,25-dihydroxyvitamin D_3; and

19-nor-26,27-dipropyl-24-trihomo-1,25-dihydroxyvitamin D_3.

Preferred estrogen agonists / antagonists of the present invention include the compounds described in U.S. patent no. 5,552,412. Those compounds are described by the formula designated herein as formula (A) given below:



(A)

wherein:

A is selected from CH_2 and NR;

B, D and E are independently selected from CH and N;

Y is

(a) phenyl, optionally substituted with 1-3 substituents independently selected from R^4;

(b) naphthyl, optionally substituted with 1-3 substituents independently selected from R^4;

(c) C_3-C_8 cycloalkyl, optionally substituted with 1-2 substituents independently selected from R^4;

(d) C_3-C_8 cycloalkenyl, optionally substituted with 1-2 substituents independently selected from R^4;

(e) a five membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, $-NR^2$- and $-S(O)_n$-, optionally substituted with 1-3 substituents independently selected from R^4;

(f) a six membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, $-NR^2$- and $-S(O)_n$- optionally substituted with 1-3 substituents independently selected from R^4; or

(g) a bicyclic ring system consisting of a five or six membered heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two heteroatoms selected from the group consisting of -O-, $-NR^2$- and $-S(O)_n$-, optionally substituted with 1-3 substituents independently selected from R^4;

Z^1 is

(a) $-(CH_2)_p W(CH_2)_q-$;

(b) $-O(CH_2)_p CR^5R^6-$;

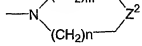
(c) $-O(CH_2)_pW(CH_2)_q-$;

(d) $-OCHR^2CHR^3-$; or

(e) $-SCHR^2CHR^3-$;

G is

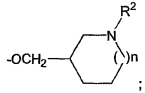
(a) $-NR^7R^8$;

(b) 

wherein n is 0, 1 or 2; m is 1, 2 or 3; Z^2 is -NH-, -O-, -S-, or $-CH_2-$; optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R^4; or

(c) a bicyclic amine containing five to twelve carbon atoms, either bridged or fused and optionally substituted with 1-3 substituents independently selected from R^4; or

Z^1 and G in combination may be



;

W is

(a) $-CH_2-$;

(b) $-CH=CH-$;

(c) $-O-$;

(d) $-NR^2-$;

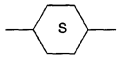
(e) $-S(O)_n-$;

(f)  ;

(g) $-CR^2(OH)-$;

(h) $-CONR^2-$;

(i) $-NR^2CO-$;

(j)  ; or

(k) $-C\equiv C-$;

R is hydrogen or C_1-C_6 alkyl;

R^2 and R^3 are independently

(a) hydrogen; or

(b) C_1-C_4 alkyl;

R^4 is

(a) hydrogen;

(b) halogen;

(c) C_1-C_6 alkyl;

(d) C_1-C_4 alkoxy;

(e) C_1-C_4 acyloxy;

(f) C_1-C_4 alkylthio;

(g) C_1-C_4 alkylsulfinyl;
(h) C_1-C_4 alkylsulfonyl;
(i) hydroxy (C_1-C_4)alkyl;
(j) aryl (C_1-C_4)alkyl;
(k) $-CO_2H$;
(l) -CN;
(m) -CONHOR;
(n) $-SO_2NHR$;
(o) $-NH_2$;
(p) C_1-C_4 alkylamino;
(q) C_1-C_4 dialkylamino;
(r) $-NHSO_2R$;
(s) $-NO_2$;
(t) -aryl; or
(u) -OH;

R^5 and R^6 are independently C_1-C_8 alkyl or together form a C_3-C_{10} carbocyclic ring;

R^7 and R^8 are independently

(a) phenyl;
(b) a C_3-C_{10} carbocyclic ring, saturated or unsaturated;
(c) a C_3-C_{10} heterocyclic ring containing up to two heteroatoms, selected from -O-, -N- and -S-;
(d) H;
(e) C_1-C_8 alkyl; or
(f) form a 3 to 8 membered nitrogen containing ring with R^5 or R^6;

R^7 and R^8 in either linear or ring form may optionally be substituted with up to three substituents independently selected from C_1-C_6 alkyl, halogen, alkoxy, hydroxy and carboxy;

a ring formed by R^7 and R^8 may be optionally fused to a phenyl ring;

e is 0, 1 or 2;

m is 1, 2 or 3;

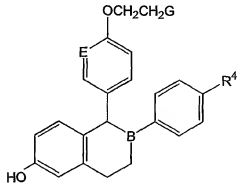
n is 0, 1 or 2;

p is 0, 1, 2 or 3;

q is 0, 1, 2 or 3;

and optical and geometric isomers thereof; and nontoxic pharmaceutically acceptable acid addition salts, N-oxides, esters, quaternary ammonium salts and prodrugs thereof.

Additional preferred estrogen agonists/antagonists are disclosed in U.S. patent no. 5,552,412 and are described by the formula designated herein as formula (Aa):



(Aa)

wherein G is

;

R^4 is H, OH, F, or Cl; and B and E are independently selected from CH and N, and optical and geometric isomers thereof; and nontoxic pharmaceutically acceptable acid addition salts, N-oxides, esters, quaternary ammonium salts and prodrugs thereof.

Especially preferred estrogen agonists/antagonists for the methods of the invention are:

cis-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

(-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

cis-1-[6'-pyrrolidinoethoxy-3'-pyridyl]-2-phenyl-6-hydroxy-1,2,3,4-tetrahydronaphthalene;

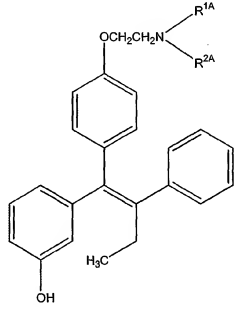
1-(4'-pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;

cis-6-(4-hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

1-(4'-pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline and pharmaceutically acceptable salts thereof.

An especially preferred salt of (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol is the D-tartrate salt.

Other preferred estrogen agonists / antagonists are disclosed in U.S. Patent 5,047,431. The structure of these compounds are described by the formula designated herein as formula (B) below:



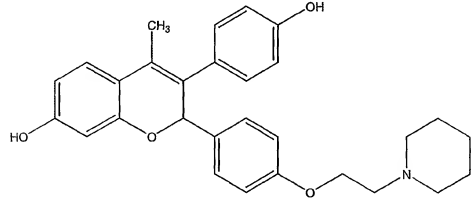
(B)

wherein

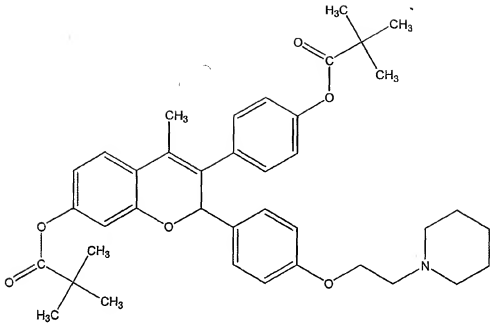
R^{1A} and R^{2A} may be the same or different and are either H, methyl, ethyl or a benzyl group; and optical or geometric isomers thereof; and pharmaceutically acceptable salts, N-oxides, esters, quaternary ammonium salts, and prodrugs thereof.

Additional preferred estrogen agonists / antagonists are the compounds disclosed in U.S. Patent No. 4,536,516; 4-hydroxy tamoxifen (i.e., tamoxifen wherein the 2-phenyl moiety has a hydroxy group at the 4 position) and other compounds as disclosed in U.S. Patent No. 4,623,660; raloxifene: (methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]-,hydrochloride) and other compounds as disclosed in U.S. Patent Numbers 4,418,068; 5,393,763; 5,457,117; 5,478,847 and 5,641,790; toremifene: (ethanamine, 2-[4-(4-chloro-1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-, (Z)-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) and other compounds as disclosed in U.S. Patent Numbers 4,696,949 and 4,996,225; centchroman: 1-[2-[[4-(-methoxy-2,2, dimethyl-3-phenyl-chroman-4-yl)-phenoxy]-ethyl]-pyrrolidine and other compounds as disclosed in U.S. Patent No. 3,822,287; idoxifene: pyrrolidine, 1-[-[4-[[1-(4-iodophenyl)-2-phenyl-1-butenyl]phenoxy]ethyl] and other compounds as disclosed in U.S. Patent No. 4,839,155; 6-(4-hydroxy-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-naphthalen-2-ol and other compounds as disclosed in U.S. Patent No. 5,484,795; and {4-[2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy]-phenyl}-[6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl]-methanone and other compounds as disclosed in published international patent application WO 95/10513. Other preferred compounds include GW 5638 and GW 7604, the synthesis of which is described in Willson et al., J. Med. Chem., 1994;37:1550-1552.

Further preferred estrogen agonists / antagonists include EM-652 (as shown in the formula designated herein as formula (C) and EM-800 (as shown in the formula designated herein as formula (D)). The synthesis of EM-652 and EM-800 and the activity of various enantiomers is described in Gauthier et al., J. Med. Chem., 1997;40:2117-2122.

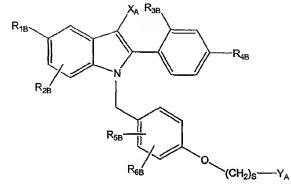


(C)

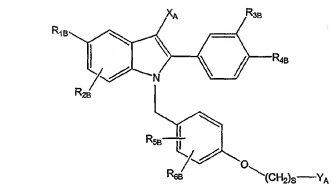


(D)

Further preferred estrogen agonists / antagonists include TSE 424 and other compounds disclosed in U.S. Patent No. 5,998,402, U.S. Patent No. 5,985,910, U.S. Patent No. 5,780,497, U.S. Patent No. 5,880,137, and European Patent Application EP 0802183 A1 including the compounds described by the formulae designated herein as formulae (E) and (F), below:



(E)



(F)

wherein:

R_{1B} is selected from H, OH or the C_1-C_{12} esters (straight chain or branched) or C_1-C_{12} (straight chain or branched or cyclic) alkyl ethers thereof, or halogens; or C_1-C_4 halogenated ethers including trifluoromethyl ether and trichloromethyl ether.

R_{2B}, R_{3B}, R_{4B}, R_{5B}, and R_{6B} are independently selected from H, OH or the C_1-C_{12} esters (straight chain or branched) or C_1-C_{12} alkyl ethers (straight chain or branched or cyclic) thereof, halogens, or C_1-C_4 halogenated ethers including trifluoromethyl ether and trichloromethyl ether, cyano, C_1-C_6 alkyl (straight chain or branched), or trifluoromethyl;

X_A is selected from H, C_1-C_6 alkyl, cyano, nitro, trifluoromethyl, and halogen;

s is 2 or 3;

Y_A is selected from:

a) the moiety:

wherein R_{7B} and R_{8B} are independently selected from the group of H, C_1-C_6 alkyl, or phenyl optionally substituted by CN, C_1-C_6 alkyl (straight chain or branched), C_1-C_6 alkoxy (straight chain or branched), halogen, -OH, $-CF_3$, or $-OCF_3$;

b) a five-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C_1-C_4 alkyl)-, -N=, and -S(O)$_u$-, wherein u is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, $-CO_2H$, -CN, $-CONHR_{1B}$, $-NH_2$, C_1-C_4 alkylamino, di(C_1-C_4)alkylamino, $-NHSO_2R_{1B}$, $-NHCOR_{1B}$, $-NO_2$, and phenyl optionally substituted with 1-3 (C_1-C_4)alkyl;

c) a six-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C_1-C_4 alkyl)-, -N=, and -S(O)$_u$-, wherein u is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, $-CO_2H$, -CN, $-CONHR_1$, $-NH_2$, C_1-C_4 alkylamino, di(C_1-C_4)alkylamino, $-NHSO_2R_{1B}$, $-NHCOR_{1B}$, $-NO_2$, and phenyl optionally substituted with 1-3 (C_1-C_4)alkyl;

d) a seven-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C_1-C_4 alkyl)-, -N=, and -S(O)$_u$-, wherein u is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, $-CO_2H$, -CN, $-CONHR_{1B}$, $-NH_2$, C_1-C_4 alkylamino,

di(C_1-C_4)alkylamino, -$NHSO_2R_{1B}$, -$NHCOR_{1B}$, -NO_2, and phenyl optionally substituted with 1-3 (C_1-C_4)alkyl; or

e) a bicyclic heterocycle containing from 6-12 carbon atoms either bridged or fused and containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C_1-C_4 alkyl)-, and -$S(O)_u$-, wherein u is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 acyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2H-, -CN-, -$CONHR_{1B}$-, -NH_2, -N=, C_1-C_4 alkylamino, di(C_1-C_4)alkylamino, -$NHSO_2R_{1B}$, -$NHCOR_{1B}$, -NO_2, and phenyl optionally substituted with 1-3 (C_1-C_4) alkyl; and optical and geometric isomers thereof; and nontoxic pharmaceutically acceptable acid addition salts, N-oxides, esters, quaternary ammonium salts, and prodrugs thereof.

Preferred compounds of this invention are those having the general structures (E) or (F), above, wherein:

R_{1B} is selected from H, OH or the C_1-C_{12} esters or alkyl ethers thereof, and halogen;

R_{2B}, R_{3B}, R_{4B}, R_{5B}, and R_{8B} are independently selected from H, OH or the C_1-C_{12} esters or alkyl ethers thereof, halogen, cyano, C_1-C_6 alkyl, or trihalomethyl, preferably trifluoromethyl, with the proviso that, when R_{1B} is H, R_{2B} is not OH;

X_A is selected from H, C_1-C_6 alkyl, cyano, nitro, trifluoromethyl, and halogen;

Y_A is the moiety:

R_{7B} and R_{8B} are selected independently from H, C_1-C_6 alkyl, or combined by -$(CH_2)_w$-, wherein w is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2H, -CN, -CONH(C_1-C_4alkyl), -NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino,

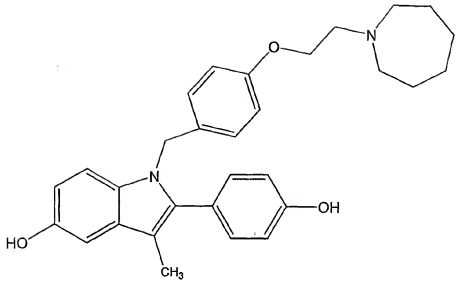
-$NHSO_2$(C_1-C_4alkyl), -CO(C_1-C_4alkyl), and -NO_2; and optical and geometric isomers thereof; and nontoxic pharmaceutically acceptable acid addition salts, N-oxides, esters, quaternary ammonium salts, and prodrugs thereof.

The rings formed by a concatenated R_{7B} and R_{8B}, mentioned above, may include, but are not limited to, aziridine, azetidine, pyrrolidine, piperidine, hexamethyleneamine or heptamethyleneamine rings.

Preferred compounds of structural formulas (E) and (F), above, are those wherein R_{1B} is OH; R_{2B} - R_{6B} are as defined above; X_A is selected from the group of Cl, NO_2, CN, CF_3, or CH_3; Y_A is the moiety

and R_{7B} and R_{8B} are concatenated together as -$(CH_2)_t$-, wherein t is an integer of from 4 to 6, to form a ring optionally substituted by up to three subsituents selected from the group of hydrogen, hydroxyl, halo, C_1-C_4 alkyl, trihalomethyl, C_1-C_4 alkoxy, trihalomethoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, hydroxy (C_1-C_4)alkyl, -CO_2H, -CN, -CONH(C_1-C_4)alkyl, -NH_2, C_1-C_4 alkylamino, di(C_1-C_4)alkylamino, -$NHSO_2$(C_1-C_4)alkyl, -NHCO(C_1-C_4)alkyl, and -NO_2; and optical and geometric isomers thereof; and nontoxic pharmaceutically acceptable acid addition salts, N-oxides, esters, quaternary ammonium salts, and prodrugs thereof.

Another preferred compound is TSE-424 as described by the formula designated herein as formula (Ea) below:



(Ea)

Another estrogen agonist/antagonist that can be used in the combination aspect of the present invention is arzoxifene, which is disclosed in U.S. patent no. 5,723,474.

The present invention is also concerned with pharmaceutical compositions and methods of treating metabolic bone disease, senile osteoporosis, postmenopausal osteoporosis, steroid induced osteoporosis, low bone turnover osteoporosis, osteomalacia, renal osteodystrophy, psoriasis, multiple sclerosis, diabetes mellitus, host versus graft rejection, transplant rejection, rheumatoid arthritis, asthma, bone fractures, bone grafts, acne, alopecia, dry skin, insufficient skin firmness, insufficient sebum secretion, wrinkles, hypertension, leukemia, colon cancer, breast cancer, prostate cancer, obesity, osteopenia, male osteoporosis, hypogonadism, andropause, frailty, muscle damage, sarcopenia, osteosarcoma, hypocalcemic tetany, hypoparathyroidism, rickets, vitamin D deficiency, anorexia, low bone mass resulting from aggressive athletic behavior, and for enhancement of peak bone mass in adolescence and prevention of second hip fracture using a combination of a 2-alkylidene-19-nor-vitamin D derivative and a pure antiestrogen. Examples of pure antiestrogens include clomiphene and trioxifene.

The present invention is also concerned with pharmaceutical compositions for the treatment of metabolic bone disease, senile osteoporosis, postmenopausal

osteoporosis, steroid induced osteoporosis, low bone turnover osteoporosis, osteomalacia, renal osteodystrophy, psoriasis, multiple sclerosis, diabetes mellitus, host versus graft rejection, transplant rejection, rheumatoid arthritis, asthma, bone fractures, bone grafts, acne, alopecia, dry skin, insufficient skin firmness, insufficient sebum secretion, wrinkles, hypertension, leukemia, colon cancer, breast cancer, prostate cancer, obesity, osteopenia, male osteoporosis, hypogonadism, andropause, frailty, muscle damage, sarcopenia, osteosarcoma, hypocalcemic tetany, hypoparathyroidism, rickets, vitamin D deficiency, anorexia, low bone mass resulting from aggressive athletic behavior, and for enhancement of peak bone mass in adolescence and prevention of second hip fracture comprising administering to a patient in need thereof a combination of a 2-alkylidene-19-nor-vitamin D derivative, such as a compound of Formula I and an estrogen agonist/antagonist or a pharmaceutically acceptable salt or prodrug thereof, and a carrier, solvent, diluent and the like.

It is noted that when compounds are discussed herein, it is contemplated that the compounds may be administered to a patient as a pharmaceutically acceptable salt, prodrug, or a salt of a prodrug. All such variations are intended to be included in the invention.

The term "patient in need thereof" means humans and other animals who have or are at risk of having metabolic bone disease, senile osteoporosis, postmenopausal osteoporosis, steroid induced osteoporosis, low bone turnover osteoporosis, osteomalacia, renal osteodystrophy, psoriasis, multiple sclerosis, diabetes mellitus, host versus graft rejection, transplant rejection, rheumatoid arthritis, asthma, bone fractures, bone grafts, acne, alopecia, dry skin, insufficient skin firmness, insufficient sebum secretion, wrinkles, hypertension, leukemia, colon cancer, breast cancer, prostate cancer, obesity, osteopenia, male osteoporosis, hypogonadism, andropause, frailty, muscle damage, sarcopenia, osteosarcoma, hypocalcemic tetany, hypoparathyroidism, rickets, vitamin D deficiency, anorexia and low bone mass resulting from aggressive athletic behavior and for enhancement of peak bone mass in adolescence and prevention of second hip fracture.

The term "treating", "treat" or "treatment" as used herein includes preventative (e.g., prophylactic), palliative and curative treatment.

By "pharmaceutically acceptable" it is meant the carrier, diluent, excipients, and/or salts or prodrugs must be compatible with the other ingredients of the formulation, and not deleterious to the patient.

An "estrogen agonist / antagonist" is a compound that affects some of the same receptors that estrogen does, but may not affect all, and in some instances, it antagonizes or blocks estrogen. It is also known as a "selective estrogen receptor modulator" (SERM). Estrogen agonists / antagonists may also be referred to as antiestrogens although they have some estrogenic activity at some target tissues. Estrogen agonists / antagonists are therefore not what are commonly referred to as "pure antiestrogens". Antiestrogens that can also act as agonists are referred to as Type I antiestrogens. Type I antiestrogens activate the estrogen receptor to bind tightly in the nucleus for a prolonged time but with impaired receptor replenishment (Clark, et al., Steroids, 1973;22:707, Capony et al., Mol Cell Endocrinol, 1975;3:233).

The term "prodrug" means a compound that is transformed *in vivo* to yield a compound of the present invention. The transformation may occur by various mechanisms, such as through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For example, when a compound of the present invention contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as (C_1-C_8)alkyl, (C_2-C_{12})alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di(C_1-C_2)alkylcarbamoyl-(C_1-C_2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl.

Similarly, when a compound of the present invention comprises an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as (C_1-C_8)alkanoyloxymethyl, 1-((C_1-C_8)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_8)alkanoyloxy)ethyl, (C_1-C_8)alkoxycarbonyloxymethyl, N-(C_1-C_8)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_8)alkanoyl, α-amino(C_1-C_4)alkanoyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, P(O)(OH)$_2$, -P(O)(O(C_1-C_6)alkyl)$_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

When a compound of the present invention comprises an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as R^X-carbonyl, R^XO-carbonyl, $NR^XR^{X_1}$-carbonyl where R^X and R^{X_1} are each independently (C_1-C_{10})alkyl, (C_3-C_7)cycloalkyl, benzyl, or R^X-carbonyl is a natural α-aminoacyl or natural α-aminoacyl-natural α-aminoacyl, -C(OH)C(O)OY^X wherein Y^X is H, (C_1-C_6)alkyl or benzyl), -C(OY^{X0}) Y^{X1} wherein Y^{X0} is (C_1-C_4) alkyl and Y^{X1} is (C_1-C_6)alkyl, carboxy(C_1-C_6)alkyl, amino(C_1-C_4)alkyl or mono-N- or di-N,N-(C_1-C_6)alkylaminoalkyl, -C(Y^{X2}) Y^{X3} wherein Y^{X2} is H or methyl and Y^{X3} is mono-N- or di-N,N-(C_1-C_6)alkylamino, morpholino, piperidin-1-yl or pyrrolidin-1-yl.

The expression "pharmaceutically acceptable salt" refers to nontoxic anionic salts containing anions such as (but not limited to) chloride, bromide, iodide, sulfate, bisulfate, phosphate, acetate, maleate, fumarate, oxalate, lactate, tartrate, citrate, gluconate, methanesulfonate and 4-toluene-sulfonate. The expression also refers to nontoxic cationic salts such as (but not limited to) sodium, potassium, calcium, magnesium, ammonium or protonated benzathine (N,N'-dibenzylethylenediamine), choline, ethanolamine, diethanolamine, ethylenediamine, meglamine (N-methyl-glucamine), benethamine (N-benzylphenethylamine), piperazine or tromethamine (2-amino-2-hydroxymethyl-1,3-propanediol).

It will be recognized that the compounds of this invention can exist in radiolabelled form, i.e., said compounds may contain one or more atoms containing an atomic mass or mass number different from the atomic mass or mass number ordinarily found in nature. Radioisotopes of hydrogen, carbon, phosphorous, fluorine and chlorine include ^{3}H, ^{14}C, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl, respectively. Compounds of this

invention which contain those radioisotopes and/or other radioisotopes of other atoms are within the scope of this invention. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, radioisotopes are particularly preferred for their ease of preparation and detectability. Radiolabelled compounds of this invention can generally be prepared by methods well known to those skilled in the art. Conveniently, such radiolabelled compounds can be prepared by carrying out the procedures disclosed herein except substituting a readily available radiolabelled reagent for a non-radiolabelled reagent.

It will be recognized by persons of ordinary skill in the art that some of the compounds of this invention have at least one asymmetric carbon atom and therefore are enantiomers or diastereomers. Diasteromeric mixtures can be separated into their individual diastereomers on the basis of their physicochemical differences by methods known *per* se as, for example, chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diasteromeric mixture by reaction with an appropriate optically active compound (e.g., alcohol), separating the diastereomers and converting (e.g., hydrolyzing, including both chemical hydrolysis methods and microbial lipase hydrolysis methods, e.g., enzyme catalyzed hydrolysis) the individual diastereomers to the corresponding pure enantiomers. All such isomers, including diastereomers, enantiomers and mixtures thereof are considered as part of this invention. Also, some of the compounds of this invention are atropisomers (e.g., substituted biaryls) and are considered as part of this invention.

In addition, when the compounds of this invention, including the compounds of Formula I or the estrogen agonist/antagonist, form hydrates or solvates, they are also within the scope of the invention.

Administration of the compounds of this invention can be via any method that delivers a compound of this invention systemically and/or locally. These methods include oral, parenteral, and intraduodenal routes, etc. Generally, the compounds of this invention are administered orally, but parenteral administration (e.g., intravenous, intramuscular, transdermal, subcutaneous, rectal or intramedullary) may be utilized, for example, where oral administration is inappropriate for the target or where the patient is unable to ingest the drug.

The compounds of this invention may also be applied locally to a site in or on a patient in a suitable carrier or diluent.

2MD and other 2-alkylidene-19-nor-vitamin D derivatives of the present invention can be administered to a human patient in the range of about 0.01 μg/day to about 10 μg/day. A preferred dosage range is about 0.05 μg/day to about 1 μg/day and a more preferred dosage range is about 0.1 μg/day to about 0.4 μg/day.

In general an effective dosage for the estrogen agonists/antagonists of this invention is in the range of 0.01 to 200 mg/kg/day, preferably 0.5 to 100 mg/kg/day.

In particular, an effective dosage for raloxifene is in the range of 0.1 to 100 mg/kg/day, preferably 0.1 to 10 mg/kg/day.

In particular, an effective dosage for tamoxifen is in the range of 0.1 to 100 mg/kg/day, preferably 0.1 to 5 mg/kg/day.

In particular, an effective dosage for 2-(4-methoxy-phenyl)-3-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]- benzo[b]thiophen-6-ol is 0.001 to 1 mg/kg/day.

In particular, an effective dosage for

cis-6-(4-fluoro-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol;

(-)-*cis*-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol;

cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol;

cis-1-(6'-pyrrolodinoethoxy-3'-pyridyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydronaphthalene;

1-(4'-pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;

cis-6-(4-hydroxyphenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol; or

1-(4'-pyrrolidinolethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline is in the range of 0.0001 to 100 mg/kg/day, preferably 0.001 to 10 mg/kg/day.

The amount and timing of administration will, of course, be dependent on the subject being treated, on the severity of the affliction, on the manner of administration and on the judgment of the prescribing physician. Thus, because of patient to patient variability, the dosages given herein are guidelines and the physician may titrate doses of the drug to achieve the treatment that the physician considers appropriate for the patient. In considering the degree of treatment

desired, the physician must balance a variety of factors such as age of the patient, presence of preexisting disease, as well as presence of other diseases. The dose may be given once a day or more than once a day and may be given in a sustained release or controlled release formulation. It is also possible to administer the compounds using a combination of an immediate release and a controlled release and/or sustained release formulation.

The administration of 2MD or other 2-alkylidene-19-nor-vitamin D derivative and an estrogen agonist/antagonist or the combination thereof can be according to any continuous or intermittent dosing schedule. Once a day, multiple times a day, once a week, multiple times a week, once every two weeks, multiple times every two weeks, once a month, multiple times a month, once every two months, once every three months, once every six months and once a year dosing are non-limiting examples of dosing schedules for 2MD or another 2-alkylidene-19-nor-vitamin D derivative and an estrogen agonist/antagonist or the combination thereof.

The compounds of the present invention are generally administered in the form of a pharmaceutical composition comprising at least one of the compounds of this invention together with a pharmaceutically acceptable vehicle or diluent. Thus, the compounds of this invention can be administered in any conventional oral, parenteral, rectal or transdermal dosage form.

For oral administration a pharmaceutical composition can take the form of solutions, suspensions, tablets, pills, capsules, powders, and the like. Tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate are employed along with various disintegrants such as starch and preferably potato or tapioca starch and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the compounds of this invention can be combined with various sweetening agents, flavoring agents, coloring agents, emulsifying agents and/or suspending agents, as well as such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof. One example of an acceptable

formulation for 2MD and other 2-alkylidene-19-nor-vitamin D derivatives is a soft gelatin capsule containing neobe oil in which the 2MD or other 2-alkylidene-19-nor-vitamin D derivative has been dissolved. Other suitable formulations will be apparent to those skilled in the art.

For purposes of parenteral administration, solutions in sesame or peanut oil or in aqueous propylene glycol can be employed, as well as sterile aqueous solutions of the corresponding water-soluble salts. Such aqueous solutions may be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose. These aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are all readily obtainable by standard techniques well-known to those skilled in the art.

For purposes of transdermal (e.g., topical) administration, dilute sterile, aqueous or partially aqueous solutions (usually in about 0.1% to 5% concentration), otherwise similar to the above parenteral solutions, are prepared.

Methods of preparing various pharmaceutical compositions with a certain amount of active ingredient are known, or will be apparent in light of this disclosure, to those skilled in this art. For examples of methods of preparing pharmaceutical compositions, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 19th Edition (1995).

Another aspect of the present invention is a kit comprising:

a. an amount of a 2-alkylidene-19-nor-vitamin D derivative, such as a compound of Formula I, and a pharmaceutically acceptable carrier or diluent in a first unit dosage form;

b. an amount of an estrogen agonist/antagonist or a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier or diluent in a second unit dosage form; and

c. a container.

The kit comprises two separate pharmaceutical compositions: a 2-alkylidene-19-nor-vitamin D derivative, such as a compound of Formula I and a second compound as described above. The kit comprises container means for containing the separate compositions such as a divided bottle or a divided foil packet, however, the separate compositions may also be contained within a single, undivided container. Typically, the kit comprises directions for the administration of the separate

components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

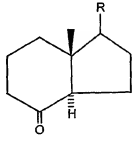
It may be desirable to provide a memory aid on the kit, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the dosage form so specified should be ingested. Another example of such a memory aid is a calendar printed on the card e.g., as follows "First Week, Monday, Tuesday, ...etc.... Second Week, Monday, Tuesday,..." etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several tablets or capsules to be taken on a given day. Also, a daily dose of a Formula I compound, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug can consist of one tablet or capsule while a daily dose of the second compound can consist of several tablets or capsules and vice versa. The memory aid should reflect this.

In another specific embodiment of the invention, a dispenser designed to dispense the daily doses one at a time in the order of their intended use is provided. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter which indicates the number of daily doses that have been dispensed.

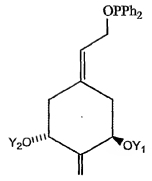
Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

The 2-alkylidene-19-nor-vitamin D derivative and an estrogen agonist/antagonist or a pharmaceutically acceptable salt or prodrug thereof can be administered in the same dosage form or in different dosage forms at the same time or at different times. All variations of administration methods are contemplated. A preferred method of administration is to administer the combination in the same dosage form at the same time. Another preferred administration method is to administer the 2-alkylidene-19-nor-vitamin D derivative in one dosage form and an estrogen agonist/antagonist or a pharmaceutically acceptable salt or prodrug thereof in another, both of which are taken at the same time.

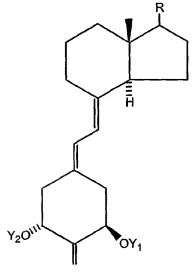
The preparation of 1α-hydroxy-2-alkyl-19-nor-vitamin D compounds, particularly 1α-hydroxy-2-methyl-19-nor-vitamin D compounds, having the basic structure I can be accomplished by a common general method, i.e., the condensation of a bicyclic Windaus-Grundmann type ketone II with the allylic phosphine oxide III to the corresponding 2-methylene-19-nor-vitamin D analogs IV followed by deprotection at C-1 and C-3 in the latter compounds:



II



III

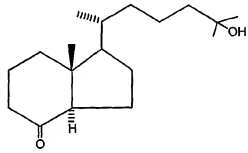


IV

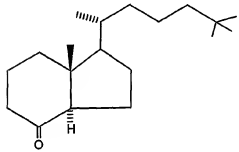
In the structures II, III, and IV groups Y_1 and Y_2 and R represent groups defined above; Y_1 and Y_2 are preferably hydroxy-protecting groups, it being also understood that any functionalities in R that might be sensitive, or that interfere with the condensation reaction, be suitably protected as is well-known in the art. The process shown above represents an application of the convergent synthesis concept, which has been applied effectively for the preparation of vitamin D compounds [e.g., Lythgoe et al., J. Chem. Soc. Perkin Trans. 1, 590 (1978); Lythgoe, Chem. Soc. Rev. 9, 449 (1983); Toh et al., J. Org. Chem. 48, 1414 (1983); Baggiolini et al., J. Org. Chem. 51, 3098 (1986); Sardina et al,. J. Org. Chem. 51, 1264 (1986); J. Org. Chem.

51, 1269 (1986); DeLuca et al., U.S. Pat. No. 5,086,191; DeLuca et al., U.S. Pat. No. 5,536,713].

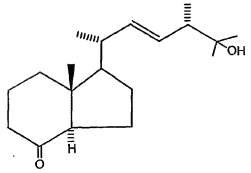
Hydrindanones of the general structure II are known, or can be prepared by known methods. Specific important examples of such known bicyclic ketones are the structures with the side chains (a), (b), (c) and (d) described above, i.e., 25-hydroxy Grundmann's ketone (f) [Baggiolini et al., J. Org. Chem. 51, 3098 (1986)]; Grundmann's ketone (g) [Inhoffen et al., Chem. Ber. 90, 664 (1957)]; 25-hydroxy Windaus ketone (h) [Baggiolini et al., J. Org. Chem. 51, 3098 (1986)] and Windaus ketone (i) [Windaus et al., Ann., 524, 297 (1936)]:



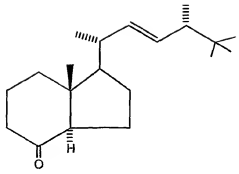
(f)



(g)



(h)



(i)

For the preparation of the required phosphine oxides of general structure III, a new synthetic route has been developed starting from methyl quinicate derivative 1, easily obtained from commercial (1R,3R,4S,5R)-(-)-quinic acid as described by Perlman et al., Tetrahedron Lett. 32, 7663 (1991) and DeLuca et al., U.S. Pat. No. 5,086,191. The overall process of transformation of the starting methyl ester 1 into the desired A-ring synthons, is summarized by the Scheme I. Thus, the secondary 4-hydroxyl group of 1 was oxidized with RuO_4 (a catalytic method with $RuCl_3$ and $NaIO_4$ as co-oxidant). Use of such a strong oxidant was necessary for an effective oxidation process of this very hindered hydroxyl. However, other more commonly used oxidants can also be applied (e.g., pyridinium dichromate), although the reactions usually require much longer time for completion. The second step of the synthesis comprises the Wittig reaction of the sterically hindered 4-keto compound 2 with the ylide prepared from methyltriphenylphosphonium bromide and n-butyllithium. Other bases can be also used for the generation of the reactive methylenephosphorane, like t-BuOK, $NaNH_2$, NaH, K/HMPT, $NaN(TMS)_2$, etc. For the preparation of the 4-methylene compound 3 some described modifications of the Wittig process can be used, e.g., reaction of 2 with activated methylenetriphenylphosphorane [Corey et al., Tetrahedron Lett. 26, 555 (1985)]. Alternatively, other methods widely used for methylenation of unreactive ketones can be applied, e.g., Wittig-Horner reaction with the PO-ylid obtained from methyldiphenylphosphine oxide upon deprotonation with n-butyllithium [Schosse et al., Chimia 30, 197 (1976)], or reaction of ketone with sodium methylsulfinate [Corey et al., J. Org. Chem. 28, 1128 (1963)] and potassium methylsulfinate [Greene et al., Tetrahedron Lett. 3755 (1976)]. Reduction of the ester 3 with lithium aluminum hydride or other suitable reducing agent (e.g., DIBALH)

provided the diol 4 which was subsequently oxidized by sodium periodate to the cyclohexanone derivative 5. The next step of the process comprises the Peterson reaction of the ketone 5 with methyl(trimethylsilyl)acetate. The resulting allylic ester 6 was treated with diisobutylaluminum hydride and the formed allylic alcohol 7 was in turn transformed to the desired A-ring phosphine oxide 8. Conversion of 7 to 8 involved 3 steps, namely, in situ tosylation with n-butyllithium and p-toluenesulfonyl chloride, followed by reaction with diphenylphosphine lithium salt and oxidation with hydrogen peroxide.

Several 2-methylene-19-nor-vitamin D compounds of the general structure IV may be synthesized using the A-ring synthon 8 and the appropriate Windaus-Grundmann ketone II having the desired side chain structure. Thus, for example, Wittig-Horner coupling of the lithium phosphinoxy carbanion generated from 8 and n-butyllithium with the protected 25-hydroxy Grundmann's ketone 9 prepared according to published procedure [Sicinski et al., J. Med. Chem. 37, 3730 (1994)] gave the expected protected vitamin compound 10. This, after deprotection with AG 50W-X4 cation exchange resin afforded 1α,25-dihydroxy-2-methylene-19-nor-vitamin D_3 (11).

The C-20 epimerization was accomplished by the analogous coupling of the phosphine oxide 8 with protected (20S)-25-hydroxy Grundmann's ketone 13 (SCHEME II) and provided 19-nor-vitamin 14 which after hydrolysis of the hydroxy-protecting groups gave (20S)-1α,25-dihydroxy-2-methylene-19-nor-vitamin D_3 (15). As noted above, other 2-methylene-19-nor-vitamin D analogs may be synthesized by the method disclosed herein. For example, 1α-hydroxy-2-methylene-19-nor-vitamin D_3 can be obtained by providing the Grundmann's ketone (g).

All documents cited in this application, including patents and patent applications, are hereby incorporated by reference. The examples presented below are intended to illustrate particular embodiments of the invention and are not intended to limit the invention, including the claims, in any manner.

Examples

The following abbreviations are used in this application.

NMR	nuclear magnetic resonance
mp	melting point
H	hydrogen
h	hour(s)

min	minutes
t-Bu	terl-butyl
THF	tetrahydrofuran
n-BuLi	n-butyl lithium
MS	mass spectra
HPLC	high pressure liquid chromatography
SEM	standard error measurement
Ph	phenyl
Me	methyl
Et	ethyl
DIBALH	diisobutylaluminum hydride
LDA	lithium diisopropylamide

The preparation of compounds of Formula I were set forth in U.S. Patent No. 5,843,928 as follows:

In these examples, specific products identified by Arabic numerals (e.g., 1, 2, 3, etc.) refer to the specific structures so identified in the preceding description and in Scheme I and Scheme II.

EXAMPLE 1

Preparation of 1α,25-dihydroxy-2-methylene-19-nor-vitamin D_3 (11)

Referring first to Scheme I the starting methyl quinicate derivative 1 was obtained from commercial (-)-quinic acid as described previously [Perlman et al., Tetrahedron Lett. 32, 7663 (1991) and DeLuca et al., U.S. Pat. No. 5,086,191]. 1:mp. 82°-82.5°C. (from hexane), ^{1}H NMR($CDCl_3$) δ 0.098, 0.110, 0.142, and 0.159 (each 3H, each s, 4x$SiCH_3$), 0.896 and 0.911 (9H and 9H, each s, 2xSi-t-Bu), 1.820 (1H, dd, J=13.1, 10.3 Hz), 2.02 (1H, ddd, J=14.3, 4.3, 2.4 Hz), 2.09 (1H, dd, J=14.3, 2.8 Hz), 2.19 (1H, ddd, J= 13.1, 4.4, 2.4 Hz), 2.31 (1H, d, J=2.8 Hz, OH), 3.42 (1H, m; after D_2O dd, J=8.6, 2.6 Hz), 3.77 (3H,s), 4.12 (1H,m), 4.37 (1H, m), 4.53 (1H,br s, OH).

(a) Oxidation of 4-hydroxy group in methyl quinicate derivative 1

(3R,5R)-3,5-Bis[(tert-butyldimethylsilyl)oxy]-1-hydroxy-4-oxocyclohexanecarboxylic Acid Methyl Ester (2). To a stirred mixture of ruthenium (III) chloride hydrate (434 mg, 2.1 mmol) and sodium periodate (10.8 g, 50.6 mmol) in water (42 mL) was added a solution of methyl quinicate 1 (6.09 g, 14 mmol) in CCl_4/CH_3CN (1:1, 64 mL). Vigorous stirring was continued for 8 h. Few drops of 2-propanol were added, the mixture was poured into water and extracted with chloroform. The organic extracts were combined, washed with water, dried ($MgSO_4$) and evaporated to give a dark oily residue (ca. 5 g) which was purified by flash chromatography. Elution with hexane/ethyl acetate (8:2) gave pure, oily 4-ketone 2 (3.4 g, 56%): ^1H NMR ($CDCl_3$) δ 0.054, 0.091, 0.127, and 0.132 (each 3H, each s, 4xSiCH_3), 0.908 and 0.913 (9H and 9H, each s, 2xSi-t-Bu), 2.22 (1H, dd, J=13.2, 11.7 Hz), 2.28 (1H, ~dt J=14.9, 3.6 Hz), 2.37 (1H, dd, J=14.9, 3.2 Hz), 2.55 (1H, ddd, J=13.2, 6.4, 3.4 Hz), 3.79 (3H,s), 4.41 (1H, t, J~3.5 Hz), 4.64 (1H, s, OH), 5.04 (1H, dd, J=11.7, 6.4 Hz); MS m/z (relative intensity) no M+, 375 (M+-t-Bu, 32), 357 (M+-t-Bu-H_2O, 47), 243 (31), 225 (57), 73 (100).

(b) Wittig reaction of the 4-ketone 2

(3R,5R)-3,5-Bis[(tert-butyldimethylsilyl)oxy]-1-hydroxy-4-methylenecyclohexanecarboxylic Acid Methyl Ester (3). To the methyltriphenylphoshonium bromide (2.813 g, 7.88 mmol) in anhydrous THF (32 mL) at 0°C. was added dropwise n-BuLi (2.5M in hexanes, 6.0 mL, 15 mmol) under argon with stirring. Another portion of $MePh_3P^+Br^-$ (2.813 g, 7.88 mmol) was then added and the solution was stirred at 0°C. for 10 min. and at room temperature for 40 min. The orange-red mixture was again cooled to 0°C. and a solution of 4-ketone 2 (1.558 g, 3.6 mmol) in anhydrous THF (16+2 mL) was siphoned to reaction flask during 20 min. The reaction mixture was stirred at 0°C. for 1 h. and at room temperature for 3h. The mixture was then carefully poured into brine cont. 1% HCl and extracted with ethyl acetate and benzene. The combined organic extracts were washed with diluted $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to give an orange oily residue (ca. 2.6 g) which was purified by flash chromatography. Elution with hexane/ethyl acetate (9:1) gave pure 4-methylene compound 3 as a colorless oil (368 mg, 24%): ^1H NMR ($CDCl_3$) δ 0.078, 0.083, 0.092, and 0.115 (each 3H, each s, 4xSiCH_3), 0.889 and 0.920 (9H and 9H, each s, 2xSi-t-Bu), 1.811 (1H, dd, J=12.6, 11.2 Hz), 2.10 (2H, m), 2.31 (1H, dd, J=12.6, 5.1 Hz), 3.76 (3H, s), 4.69 (1H, t, J=3.1 Hz), 4.78 (1H, m), 4.96 (2H, m; after D_2O 1H, br s), 5.17 (1H, t, J=1.9 Hz); MS m/z (relative intensity) no M+,

373 (M+-t-Bu, 57), 355 (M+-t-Bu $-H_2O$, 13), 341 (19), 313 (25), 241 (33), 223 (37), 209 (56), 73 (100).

(c) Reduction of ester group in the 4-methylene compound 3 [(3R,5R)-3,5-Bis[(tert-butyldimethylsilyl)oxy]-1-hydroxy-4-methylenecyclohexyl]methanol (4). (i) To a stirred solution of the ester 3 (90 mg, 0.21 mmol) in anhydrous THF (8 mL) lithium aluminum hydride (60 mg, 1.6 mmol) was added at 0°C. under argon. The cooling bath was removed after 1 h. and the stirring was continued at 6°C. for 12 h. and at room temperature for 6 h. The excess of the reagent was decomposed with saturated aq. Na_2SO_4, and the mixture was extracted with ethyl acetate and ether, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue with hexane/ethyl acetate (9:1) afforded unreacted substrate (12 mg) and a pure, crystalline diol 4 (35 mg, 48% based on recovered ester 3): ^1H NMR ($CDCl_3+D_2O$) δ 0.079, 0.091, 0.100, and 0.121 (each 3H, each s, 4xSiCH_3), 0.895 and 0.927 (9H and 9H, each s, 2xSi-t-Bu), 1.339 (1H, t, J~12 Hz), 1.510 (1H, dd, J=14.3, 2.7 Hz), 2.10 (2H, m), 3.29 and 3.40 (1H and 1H, each d, J=11.0 Hz), 4.66 (1H, t, J~2.8 Hz), 4.78 (1H, m), 4.92 (1H, t, J=1.7 Hz), 5.13 (1H, t, J=2.0 Hz); MS m/z (relative intensity) no M+, 345 (M+-t-Bu, 8), 327 (M+-t-Bu-H_2O, 22), 213 (28), 195 (11), 73 (100).

(ii) Diisobutylaluminum hydride (1.5M in toluene, 2.0 mL, 3 mmol) was added to a solution of the ester 3 (215 mg, 0.5 mmol) in anhydrous ether (3 mL) at –78°C. under argon. The mixture was stirred at –78°C. for 3 h. and at –24°C. for 1.5 h., diluted with ether (10 mL) and quenched by the slow addition of 2N potassium sodium tartrate. The solution was warmed to room temperature and stirred for 15 min., the poured into brine and extracted with ethyl acetate and ether. The organic extracts were combined, washed with diluted (ca. 1%) HCl, and brine, dried ($MgSO_4$) and evaporated. The crystalline residue was purified by flash chromatography. Elution with hexane/ethyl acetate (9:1) gave crystalline diol 4 (43 mg, 24%).

(d) Cleavage of the vicinal diol 4

(3R,5R)-3,5-Bis[(tert-butyldimethylsilyl)oxy]-4-methylenecyclohexanone (5). Sodium periodate saturated water (2.2 mL) was added to a solution of the diol 4 (146 mg, 0.36 mmol) in methanol (9 mL) at 0°C. The solution was stirred at 0°C. for 1 h., poured into brine and extracted with ether and benzene. The organic extracts were combined, washed with brine, dried ($MgSO_4$) and evaporated. An oily residue was

dissolved in hexane (1 mL) and applied on a silica Sep-Pak cartridge. Pure 4-methylenecyclohexanone derivative 5 (110 mg, 82%) was eluted with hexane/ethyl acetate (95:5) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.050 and 0.069 (6H and 6H, each s, 4xSiCH_3), 0.881 (18H, s, 2xSi-t-Bu), 2.45 (2H, ddd, J=14.2, 6.9, 1.4 Hz), 2.64 (2H, ddd, J=14.2, 4.6, 1.4 Hz), 4.69 (2H, dd, J=6.9, 4.6 Hz), 5.16 (2H, s); MS M/z (relative intensity) no M+, 355 (M+-Me, 3), 313 (M+-t-Bu, 100), 73 (76).

(e) Preparation of the allylic ester 6

[(3'R,5'R)-3',5'-Bis[(tert-butyldimethylsilyl)oxy]-4'-methylenecyclohexylidene]acetic Acid Methyl Ester (6). To a solution of diisopropylamine (37 μL, 0.28 mmol) in anhydrous THF (200 μL) was added n-BuLi (2.5M in hexanes, 113 μL, 0.28 mmol) under argon at –788 C. with stirring, and methyl(trimethylsilyl)acetate (46 μL, 0.28 mmol) was then added. After 15 min., the keto compound 5 (49 mg, 0.132 mmol) in anhydrous THF (200+80 μL) was added dropwise. The solution was stirred at –78°C. for 2 h. and the reaction mixture was quenched with saturated NH_4Cl, poured into brine and extracted with ether and benzene. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was dissolved in hexane (1 mL) and applied on a silica Sep-Pak cartridge. Elution with hexane and hexane/ethyl acetate (98:2) gave a pure allylic ester 6 (50 mg, 89%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.039, 0.064, and 0.076 (6H, 3H, and 3H, each s, 4xSiCH_3), 0.864 and 0.884 (9H and 9H, each s, 2xSi-t-Bu), 2.26 (1H, dd, J=12.8, 7.4 Hz), 2.47 (1H, dd, J=12.8, 4.2 Hz), 2.98 (1H, dd, J=13.3, 4.0 Hz), 3.06 (1H, dd, J=13.3, 6.6 Hz), 3.69 (3H, s), 4.48 (2H, m), 4.99 (2H, s), 5.74 (1H, s); MS m/z (relative intensity) 426 (M+, 2), 411 (M+-Me, 4), 369 (M+-t-Bu, 100), 263 (69).

(f) Reduction of the allylic ester 6

2-[(3'R,5'R)-3',5'-Bis[(tert-butyldimethylsilyl)oxy]-4'-methylenecyclohexylidene]ethanol (7). Diisobutylaluminum hydride (1.5M in toluene, 1.6 mL, 2.4 mmol) was slowly added to a stirred solution of the allylic ester 6 (143 mg, 0.33 mmol) in toluene/methylene chloride (2:1, 5.7 mL) at –78°C. under argon. Stirring was continued as –78°C. for 1 h. and at –46°C. (cyclohexanone/dry ice bath) for 25 min. The mixture was quenched by the slow addition of potassium sodium tartrate (2N, 3 mL), aq. HCl (2N, 3 mL) and H_2O (12 mL), and then diluted with methylene chloride (12 mL) and extracted with ether and benzene. The organic extracts were combined, washed with diluted (ca. 1%) HCl, and brine, dried ($MgSO_4$)

and evaporated. The residue was purified by flash chromatography. Elution with hexane/ethyl acetate (9:1) gave crystalline allylic alcohol 7 (130 mg, 97%): ^{1}H NMR ($CDCl_3$) δ 0.038, 0.050, and 0.075 (3H, 3H, and 6H, each s, 4xSiCH$_3$), 0.876 and 0.904 (9H and 9H, each s, 2xSi-t-Bu), 2.12 (1H, dd J=12.3, 8.8 Hz), 2.23 (1H, dd, J=13.3, 2.7 Hz), 2.45 (1H, dd, J=12.3, 4.8 Hz), 2.51 (1H, dd, J=13.3, 5.4 Hz), 4.04 (1H, m; after D_2O dd, J=12.0, 7.0 Hz), 4.17 (1H, m; after D_2O dd, J=12.0, 7.4 Hz), 4.38 (1H, m), 4.49 (1H, m), 4.95 (1H, br s), 5.05 (1H, t, J=1.7 Hz), 5.69 (1H, ~t, J=7.2 Hz); MS m/z (relative intensity) 398 (M+, 2), 383 (M+-Me, 2), 365 (M+-Me-H_2O, 4), 341 (M+-t-Bu, 78), 323 (M+-t-Bu-H_2O, 10), 73 (100).

(g) Conversion of the allylic alcohol 7 into phosphine oxide 8 [2-[(3'R,5'R)-3',5'-Bis[(tert-butyldimethylsilyl)oxy]-4'-methylenecyclohexylidene]ethyl]diphenylphosphine Oxide (8). To the allylic alcohol 7 (105 mg, 0.263 mmol) in anhydrous THF (2.4 mL) was added n-BuLi (2.5M in hexanes, 105 μL, 0.263 mmol) under argon at 0°C. Freshly recrystallized tosyl chloride (50.4 mg, 0.264 mmol) was dissolved in anhydrous THF (480 μL) and added to the allylic alcohol-BuLi solution. The mixture was stirred at 0°C. for 5 min. and set aside at 0°C. In another dry flask with air replaced by argon, n-BuLi (2.5M in hexanes, 210 μL, 0.525 mmol) was added to Ph_2PH (93 μL, 0.534 mmol in anhydrous THF (750 μL) at 0°C. with stirring. The red solution was siphoned under argon pressure to the solution of tosylate until the orange color persisted (ca. ½ of the solution was added). The resulting mixture was stirred an additional 30 min. at 0°C., and quenched by addition of H_2O (30 μL). Solvents were evaporated under reduced pressure and the residue was redissolved in methylene chloride (2.4 mL) and stirred with 10% H_2O_2 at 0°C. for 1 h. The organic layer was separated, washed with cold aq. Sodium sulfite and H_2O, dried ($MgSO_4$) and evaporated. The residue was subject to flash chromatography. Elution with benzene/ethyl acetate (6:4) gave semicrystalline phosphine oxide 8 (134 mg, 87%): ^{1}H NMR ($CDCl_3$) δ 0.002, 0.011 and 0.019 (3H, 3H, and 6H, each s, 4xSiCH$_3$), 0.855 and 0.860 (9H and 9H, each s, 2xSi-t-Bu), 2.0-2.1 (3H, br m), 2.34 (1H, m), 3.08 (1H, m), 3.19 (1H, m), 4.34 (2H, m), 4.90 and 4.94 (1H and 1H, each s,), 5.35 (1H, ~q, J=7.4 Hz), 7.46 (4H, m), 7.52 (2H, m), 7.72 (4H, m); MS m/z (relative intensity) no M+, 581 (M+-1, 1), 567 (M+-Me, 3) 525 (M+-t-Bu, 100), 450 (10), 393 (48).

(h) Wittig-Horner coupling of protected 25-hydroxy Grundmann's ketone 9 with the phosphine oxide 8

1α,25-Dihydroxy-2-methylene-19-nor-vitamin D_3 (11). To a solution of phosphine oxide 8 (33.1 mg, 56.8 μmol) in anhydrous THF (450 μL) at 0°C. was slowly added n-BuLi (2.5M in hexanes, 23 μL, 57.5 μmol) under argon with stirring. The solution turned deep orange. The mixture was cooled to –78°C. and a precooled (-78°C.) solution of protected hydroxy ketone 9 (9.0 mg, 22.8 μmol), prepared according to published procedure [Sicinski et al., J. Med. Chem. 37, 3730 (1994)], in anhydrous THF (200+100 μL) was slowly added. The mixture was stirred under argon at –78°C. for 1 h. and at 0°C. for 18 h. Ethyl acetate was added, and the organic phase was washed with brine, dried ($MgSO_4$) and evaporated. The residue was dissolved in hexane and applied on a silica Sep-Pak cartridge, and washed with hexane/ethyl acetate (99:1, 20 mL) to give 19-nor-vitamin derivative 10 (13.5 mg, 78%). The Sep-Pak was then washed with hexane/ethyl acetate (96:4), 10 mL) to recover some unchanged C,D-ring ketone 9 (2 mg), and with ethyl acetate (10 mL) to recover diphenylphosphine oxide (20 mg). For analytical purpose a sample of protected vitamin 10 was further purified by HPLC (6.2 mm x 25 cm Zorbax-Sil column, 4 mL/min) using hexane/ethyl acetate (99.9:0.1) solvent system. Pure compound 10 was eluted at R_v 26 mL as a colorless oil: UV (in hexane) λ_{max} 224, 253, 263 nm; ^1H NMR ($CDCl_3$) δ 0.025, 0.049, 0.066, and 0.080 (each 3H, each s, 4x$SiCH_3$); 0.546 (3H, s, 18-H_3), 0.565 (6H, q, J=7.9 Hz, 3x$SiCH_2$), 0.864 and 0.896 (9H and 9H, each s, 2xSi-t-Bu), 0.931 (3H, d, J=6.0 Hz, 21-H_3), 0.947 (9H, t, J=7.9 Hz, 3x$SiCH_2CH_3$), 1.188 (6H, s, 26- and 27-H_3), 2.00 (2H, m), 2.18 (1H, dd, J=12.5, 8.5 Hz, 4β-H), 2.33 (1H, dd, J=13.1, 2.9 Hz, 10β-H), 2.46 (1H, dd J=12.5, 4.5 Hz, 4α-H), 2.52 (1H, dd, J=13.1, 5.8 Hz, 10α-H), 2.82 (1H, br d, J=12 Hz, 9β-H), 4.43 (2H, m, 1β- and 3α-H), 4.92 and 4.97 (1H and 1H, each s, $=CH_2$), 5.84 and 6.22 (1H and 1H, each d, J=11.0 Hz, 7- and 6-H); MS m/z (relative intensity) 758 (M+, 17), 729 (M+-Et, 6), 701 (M+-t-Bu, 4), 626 (100), 494 (23), 366 (50), 73 (92).

Protected vitamin 10 (4.3 mg) was dissolved in benzene (150 μL) and the resin (AG 50W-X4, 60 mg; prewashed with methanol) in methanol (800 μL) was added. The mixture was stirred at room temperature under argon for 17 h., diluted with ethyl acetate/ether (1:1, 4 mL) and decanted. The resin was washed with ether (8 mL) and

the combined organic phases washed with brine and saturated $NaHCO_3$, dried ($MgSO_4$) and evaporated. The residue was purified by HPLC (62 mm x 25 cm Zorbax-Sil column, 4 mL/min.) using hexane/2-propanol (9:1) solvent system. Analytically pure 2-methylene-19-nor-vitamin 11 (2.3 mg, 97%) was collected at R_v 29 mL (1α,25-dihydroxyvitamin D_3 was eluted at R_v 52 mL in the same system) as a white solid: UV (in EtOH) λ_{max} 243.5, 252, 262.5 nm; ^1H NMR ($CDCl_3$) δ 0.552 (3H, s, 18-H_3), 0.941 (3H, d, J=6.4 Hz, 21-H_3), 1.222 (6H, s, 26- and 27-H_3), 2.01 (2H, m), 2.27-2.36 (2H, m), 2.58 (1H, m), 2.80-2.88 (2H, m), 4.49 (2H, m, 1β- and 3α-H), 5.10 and 5.11 (1H and 1H, each s, $=CH_2$), 5.89 and 6.37 (1H and 1H, each d, J=11.3 Hz, 7- and 6-H); MS m/z (relative intensity) 416 (M+, 83), 398 (25), 384 (31), 380 (14), 351 (20), 313 (100).

EXAMPLE 2

Preparation of (20S)-1α,25-dihydroxy-2-methylene-19-nor-vitamin D_3 (15)

Scheme II illustrates the preparation of protected (20S)-25-hydroxy Grundmann's ketone 13, and its coupling with phosphine oxide 8 (obtained as described in Example 1).

(a) Silylation of hydroxy ketone 12

(20S)-25-[(Triethylsilyl)oxy]-des-A,B-cholestan-8-one (13). A solution of the ketone 12 (Tetrionics, Inc. Madison, WI.; 56 mg, 0.2 mmol) and imidazole (65 mg, 0.95 mmol) in anhydrous DMF (1.2 mL) was treated with triethylsilyl chloride (95 μL, 0.56 mmol), and the mixture was stirred at room temperature under argon for 4 h. Ethyl acetate was added and water, and the organic layer was separated. The ethyl acetate layer was washed with water and brine, dried ($MgSO_4$) and evaporated. The residue was passed through a silica Sep-Pak cartridge in hexane/ethyl acetate (9:1) and after evaporation, purified by HPLC (9.4 mm x 25 cm Zorbax-Sil column, 4 mL/min) using hexane/ethyl acetate (9:1) solvent system. Pure protected hydroxy ketone 13 (55mg, 70%) was eluted at R_v 35 mL as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.566 (6H, q, J=7.9 Hz, 3xSiCH_2), 0.638 (3H, s, 18-H_3), 0.859 (3H, d, J=6.0 Hz, 21-H_3), 0.947 (9H, t, J=7.9 Hz, 3xSiCH_2CH_3), 1.196 (6H, s, 26- and 27-H_3), 2.45 (1H, dd, J=11.4, 7.5 Hz, 14α-H).

(b) Wittig-Horner coupling of protected (20S)-25-hydroxy Grundmann's ketone 13 with the phosphine oxide 8

(20S)-1α,25-Dihydroxy-2-methylene-19-nor-vitamine D_3 (15). To a solution of phosphine oxide 8 (15.8 mg, 27.1 μmol) in anhydrous THF (200 μL) at 0°C. was slowly added n-BuLi (2.5M in hexanes, 11 μL, 27.5 μmol) under argon with stirring. The solution turned deep orange. The mixture was cooled to –78°C. and a precooled (-78°C.) solution of protected hydroxy ketone 13 (8.0 mg, 20.3 μmol) in anhydrous THF (100 μL) was slowly added. The mixture was stirred under argon at –78°C. for 1 h. and at 0°C. for 18 h. Ethyl acetate was added, and the organic phase was washed with brine, dried ($MgSO_4$) and evaporated. The residue was dissolved in hexane and applied on a silica Sep-Pak cartridge, and washed with hexane/ethyl acetate (99.5:0.5, 20 mL) to give 19-nor-vitamin derivative 14 (7 mg, 45%) as a colorless oil. The Sep-Pak was then washed with hexane/ethyl acetate (96:4, 10 mL) to recover some unchanged C,D-ring ketone 13 (4 mg), and with ethyl acetate (10 mL) to recover diphenylphosphine oxide (9 mg). For analytical purpose a sample of protected vitamin 14 was further purified by HPLC (6.2 mm x 25 cm Zorbax-Sil column, 4 mL/min) using hexane/ethyl acetate (99.9:0.1) solvent system.

14: UV (in hexane) λ_{max} 244, 253.5, 263 nm; ^1H NMR ($CDCl_3$) δ 0.026, 0.049, 0.066 and 0.080 (each 3H, each s, 4x$SiCH_3$), 0.541 (3H, s, 18-H_3), 0.564 (6H, q, J=7.9 Hz, 3x$SiCH_2$), 0.848 (3H, d, J=6.5 Hz, 21-H_3), 0.864 and 0.896 (9H and 9H, each s, 2xSi-t-Bu), 0.945 (9H, t, J=7.9 Hz, 3x$SiCH_2CH_3$), 1.188 (6H, s, 26- and 27-H_3), 2.15-2.35 (4H, br m), 2.43-2.53 (3H, br m), 2.82 (1H, br d, J=12.9 Hz, 9β-H), 4.42 (2H, m, 1β- and 3α-H), 4.92 and 4.97 (1H and 1H, each s, =CH_2), 5.84 and 6.22 (1H and 1H, each d, J=11.1 Hz, 7- and 6-H); MS m/z (relative intensity) 758 (M+, 33), 729 (M+-Et, 7), 701 (M+-t-Bu, 5), 626 (100), 494 (25), 366 (52), 75 (82), 73 (69).

Protected vitamin 14 (5.0 mg) was dissolved in benzene (160 μL) and the resin (AG 50W-X4, 70 mg; prewashed with methanol) in methanol (900 μL) was added. The mixture was stirred at room temperature under argon for 19 h. diluted with ethyl acetate/ether (1:1, 4 mL) and decanted. The resin was washed with ether (8 mL) and the combined organic phases washed with brine and saturated $NaHCO_3$, dried ($MgSO_4$) and evaporated. The residue was purified by HPLC (6.2 mm x 25 cm Zorbax-Sil column, 4 mL/min.) using hexane/2-propanol (9:1) solvent system. Analytically pure 2-methylene-19-nor-vitamin 15 (2.6 mg, 95%) was collected at R_v 28

mL [(20R)-analog was eluted at R_v 29 mL and 1α,25-dihydroxyvitamin D_3 at R_v 52 mL in the same system] as a white solid: UV (in EtOH) λ_{max} 243.5, 252.5, 262.5nm; ^1H NMR ($CDCl_3$) δ 0.551 (3H, s, 18-H_3), 0.858 (3H, d, J=6.6 Hz, 21-H_3), 1.215 (6H, s, 26- and 27-H_3), 1.95-2.04 (2H, m), 2.27-2.35 (2H, m), 2.58 (1H, dd, J=13.3, 3.0 Hz), 2.80-2.87 (2H, m), (2H, m, 1β- and 3α-H), 5.09 and 5.11 (1H and 1H, each s, =CH_2), 5.89 and 6.36 (1H and 1H, each d, J=11.3 Hz, 7- and 6-H); MS m/z (relative intensity) 416 (M+, 100), 398 (26), 380 (13), 366 (21), 313 (31).

BIOLOGICAL ACTIVITY OF 2-METHYLENE-SUBSTITUTED 19-NOR-1,25-$(OH)_2D_3$ COMPOUNDS AND THEIR 20S-ISOMERS

The biological activity of compounds of Formula I was set forth in U.S. Patent No. 5,843,928 as follows. The introduction of a methylene group to the 2-position of 19-nor-1,25-$(OH)_2D_3$ or its 20S-isomer had little or no effect on binding to the porcine intestinal vitamin D receptor. All compounds bound equally well to the porcine receptor including the standard 1,25-$(OH)_2D_3$. It might be expected from these results that all of the compounds would have equivalent biological activity. Surprisingly, however, the 2-methylene substitutions produced highly selective analogs with their primary action on bone. When given for 7 days in a chronic mode, the most potent compound tested was the 2-methylene-19-nor-20S-1,25-$(OH)_2D_3$ (Table 1). When given at 130 pmol/day, its activity on bone calcium mobilization (serum calcium) was of the order of at least 10 and possible 100-1,000 times more than that of the native hormone. Under identical conditions, twice the dose of 1,25-$(OH)_2D_3$ gave a serum calcium value of 13.8 mg/100 ml of serum calcium at the 130 pmol dose. When given at 260 pmol/day, it produced the astounding value of 14 mg/100 ml of serum calcium at the expense of bone. To show its selectivity, this compound produced no significant change in intestinal calcium transport at either the 130 or 260 pmol dose, while 1,25-$(OH)_2D_3$ produced the expected elevation of intestinal calcium transport at the only dose tested, i.e. 260 pmol/day. The 2-methylene-19-nor-1,25-$(OH)_2D_3$ also had extremely strong bone calcium mobilization at both dose levels but also showed no intestinal calcium transport activity. The bone calcium mobilization activity of this compound is likely to be 10-100 times that of 1,25-$(OH)_2D_3$. These results illustrate that the 2-methylene and the 20S-2-methylene derivatives of 19-nor-1,25-$(OH)_2D_3$ are selective for the mobilization of calcium from

bone. Table 2 illustrates the response of both intestine and serum calcium to a single large dose of the various compounds; again, supporting the conclusions derived from Table 1.

The results illustrate that 2-methylene-19-nor-20S-1,25-$(OH)_2D_3$ is extremely potent in inducing differentiation of HL-60 cells to the monocyte. The 2-methylene-19-nor compound had activity similar to 1,25-$(OH)_2D_3$. These results illustrate the potential of the 2-methylene-19-nor-20S-1,25-$(OH)_2D_3$ and 2-methylene-19-nor-1,25-$(OH)_2D_3$ compounds as anti-cancer agents, especially against leukemia, colon cancer, breast cancer and prostate cancer, or as agents in the treatment of psoriasis.

Competitive binding of the analogs to the porcine intestinal receptor was carried out by the method described by Dame et al. (Biochemistry 25, 4523-4534, 1986).

The differentiation of HL-60 promyelocytic into monocytes was determined as described by Ostrem et al (J. Biol. Chem. 262, 14164-14171, 1987).

TABLE 1

Response of Intestinal Calcium Transport and Serum Calcium (Bone Calcium Mobilization) Activity to Chronic Doses of 2-Methylene Derivatives of 19-Nor-1,25-$(OH)_2D_3$ and its 20S Isomers

Group	Dose (pmol/day/7 days)	Intestinal Calcium Transport (S/M)	Serum Calcium (mg/100 ml)
Vitamin D Deficient	Vehicle	5.5 ± 0.2	5.1 ± 0.16
1,25-$(OH)_2D_3$ Treated	260	6.2 ± 0.4	7.2 ± 0.5
2-Methylene-19-Nor-1,25-$(OH)_2D_3$	130	5. 3 ± 0.4	9.9 ± 0.2
	260	4.9 ± 0.6	9.6 ± 0.3
2-Methylene-19-Nor-20S-1,25-$(OH)_2D_3$	130	5.7 ± 0.8	13.8 ± 0.5
	260	4.6 ± 0.7	14.4 ± 0.6

Male weanling rats were obtained from Sprague Dawley Co. (Indianapolis, Ind.) and fed a 0.47% calcium, 0.3% phosphorus vitamin D-deficient diet for 1 week and then given the same diet containing 0.02% calcium, 0.3% phosphorus for 2 weeks. During the last week they were given the indicated dose of compound by intraperitoneal injection in 0.1 ml 95% propylene glycol and 5% ethanol each day for 7 days. The control animals received only the 0.1 ml of 95% propylene glycol, 5%

ethanol. Twenty-four hours after the last dose, the rats were sacrificed and intestinal calcium transport was determined by everted sac technique as previously described and serum calcium determined by atomic absorption spectrometry on a model 3110 Perkin Elmer instrument (Norwalk, Conn.). There were 5 rats per group and the values represent mean (±)SEM.

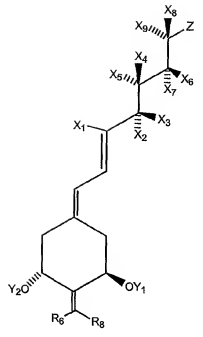
TABLE 2

Response of Intestinal Calcium Transport and Serum Calcium (Bone Calcium Mobilization) Activity to Chronic Doses of 2-Methylene Derivatives of 19-Nor-1,25-$(OH)_2D_3$ and its 20S Isomers

Group	Intestinal Calcium Transport (S/M)	Serum Calcium (mg/100 ml)
-D Control	4.2 ± 0.3	4.7 ± 0.1
1,25-$(OH)_2D_3$	5.8 ± 0.3	5.7 ± 0.2
2-Methylene-19-Nor-1,25-$(OH)_2D_3$	5.3 ± 0.5	6.4 ± 0.1
2-Methylene-19-Nor-20S-1,25-$(OH)_2D_3$	5.5 ± 0.6	8.0 ± 0.1

Male Holtzman strain weanling rats were obtained from the Sprague Dawley Co. (Indianapolis, Ind.) and fed the 0.47% calcium, 0.3% phosphorus diet described by Suda et al. (J. Nutr. 100, 1049-1052, 1970) for 1 week and then fed the same diet containing 0.02% calcium and 0.3% phosphorus for 2 additional weeks. At this point, they received a single intrajugular injection of the indicated dose dissolved in 0.1 ml of 95% propylene glycol/5% ethanol. Twenty-four hours later they were sacrificed and intestinal calcium transport and serum calcium were determined as described in Table 1. The dose of the compounds was 650 pmol and there were 5 animals per group. The data are expressed as mean (±)SEM.

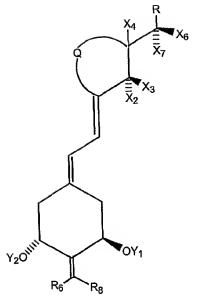
Accordingly, compounds of the following formulae Ia, are along with those of formula I, also encompassed by the present invention:



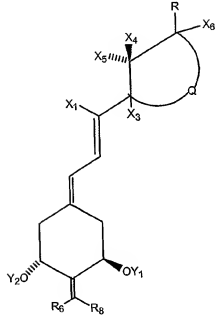
Ia

In the above formula Ia, the definitions of Y_1, Y_2, R_6, R_8 and Z are as previously set forth herein. With respect to X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8 and X_9, these substituents may be the same or different and are selected from hydrogen or lower alkyl, i.e., a $C_{1\text{-}5}$ alkyl such as a methyl, ethyl or n-propyl. In addition, paired substituents X_1 and X_4, or X_5, X_2 or X_3 and X_6 or X_7, X_4 or X_5 and X_8 or X_9, when taken together with the three adjacent carbon atoms of the central part of the compound, which correspond to positions 8, 14, 13 or 14, 13, 17 or 13, 17, 20 respectively, can be the same or different and form a saturated or unsaturated, substituted or unsubstituted, carbocyclic 3, 4, 5, 6 or 7 membered ring.

Preferred compounds of the present invention may be represented by one of the following formulae:

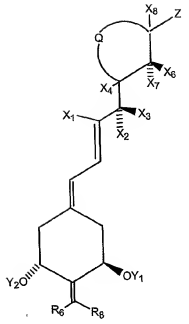


Ib

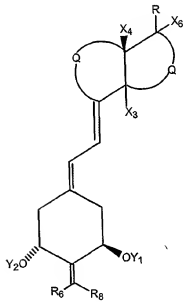


Ic

5

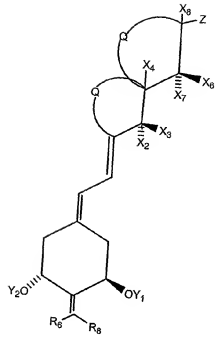


Id

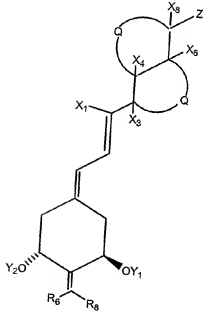


Ie

5

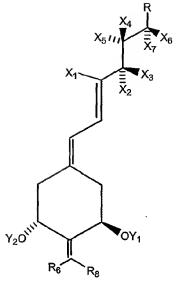


If



Ig

5

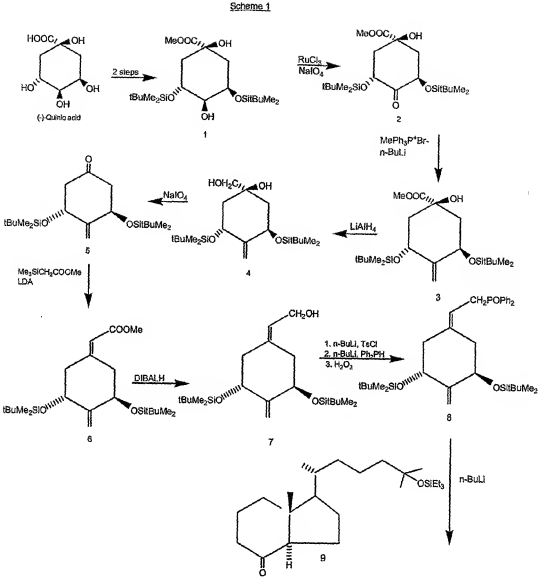


Ih

In the above formulae Ib, Ic, Id, Ie, If, Ig and Ih, the definitions of Y_1, Y_2, R_6, R_8, R, Z, X_1, X_2, X_3, X_4, X_5, X_6, X_7, and X_8 are as previously set forth herein. The substituent Q represents a saturated or unsaturated, substituted or unsubstituted, hydrocarbon chain comprised of 0, 1, 2, 3 or 4 carbon atoms, but is preferably the group $-(CH_2)_k-$ where k is an integer equal to 2 or 3.

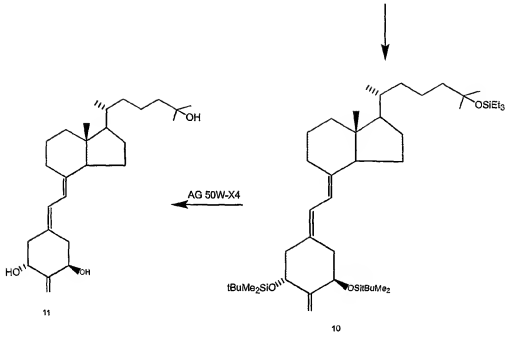
Methods for making compounds of formulae Ia-Ih are known. Specifically, reference is made to International Application Number PCT/EP94/02294 filed July 7, 1994, and published January 19, 1995, under International Publication Number WO95/01960.

Scheme 1


HOOC
OH
HO
OH
OH
(-)-Quinic acid
2 steps
MeOOC
OH
tBuMe2SiO
OSitBuMe2
OH
1
RuCl3
NaIO4
MeOOC
OH
tBuMe2SiO
OSitBuMe2
O
2
MePh3P+Br-
n-BuLi
MeOOC
OH
tBuMe2SiO
OSitBuMe2
3
LiAlH4
HOH2C
OH
tBuMe2SiO
OSitBuMe2
4
NaIO4
O
tBuMe2SiO
OSitBuMe2
5
Me3SiCH2COOMe
LDA
COOMe
tBuMe2SiO
OSitBuMe2
6
DIBALH
CH2OH
tBuMe2SiO
OSitBuMe2
7
1. n-BuLi, TsCl
2. n-BuLi, Ph2PH
3. H2O2
CH2POPh2
tBuMe2SiO
OSitBuMe2
8
OSiEt3
n-BuLi
O
H
H
9

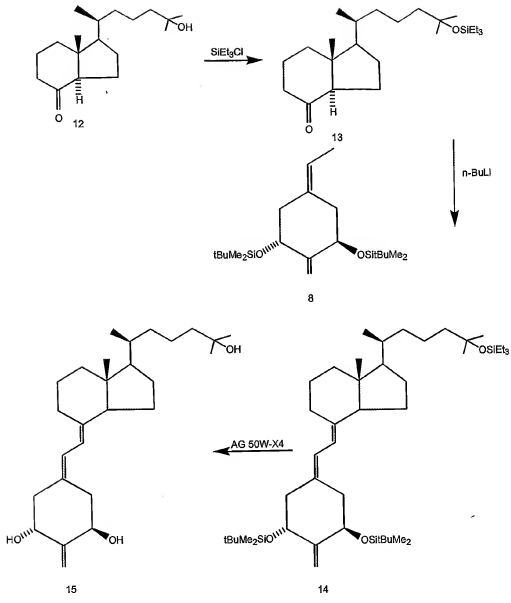
5

Scheme 1 (continued)



11 10

Scheme II


OH
SiEt3Cl
OSiEt3
H
O
12
13
n-BuLi
tBuMe2SiO
OSitBuMe2
8
AG 50W-X4
HO
15
14

5

EXAMPLES OF THE SYSNTHESIS AND FORMUATION OF *CIS-6-PHENYL-5-[4-(2-PYRROLIDIN-1-YLETHOXY)PHENYL]-5,6,7,8-TETRAHYDRONAPHTHALEN-2-OL, D-TRATRATE*

Preparation of cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol ("lasofoxifene"):

Lasofoxifene was prepared as described in U.S. Patent No. 5,552,412 and reproduced below.

A solution of 1-[2-[4-(6-methoxy-2-phenyl-3,4 dihydronaphthalen-1-yl)phenoxy]ethyl]pyrrolidine hydrochloride (nafoxidene hydrochloride) (1.0 g, 2.16 mmol) in 20 mL of absolute ethanol containing 1.0 g of palladium hydroxide on carbon was hydrogenated at 60 psi (0.41 MPa) at 20°C for 19 hr. Filtration and evaporation provided 863 mg (93%) of *cis*-1-[2-[4-(6-methoxy-2-phenyl 1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy] ethyl} pyrrolidine.

^{1}H-NMR ($CDCl_3$.): δ 3.50-3.80 (m, 3H), 3.85 (s, 3H), 4.20-4.40 (m, 3H), 6.80-7.00 (m, 3H); MS 428 (P^{+1}).

To a solution of 400 mg (0.94 mmol) of *cis*-1-{2-[4-(6-methoxy-2-phenyl 1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy] ethyl} pyrrolidine in 25 mL of methylene chloride at 0°C was added, dropwise with stirring, 4.7 ml (4.7 mmol) of a 1.0 M solution of boron tribromide in methylene chloride. After 3 hours at room temperature, the reaction was poured into 100 mL of rapidly stirring saturated aqueous sodium bicarbonate. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated to afford 287 mg (74% yield) of lasofoxifene as the free base.

^{1}H-NMR ($CDCl_3$): δ 3.35 (dd, 1H), 4.00 (t, 2H), 4.21 (d, 1H), 6.35 (ABq, 4H).

The corresponding hydrochloride salt was prepared by treating a solution of the base with excess 4N HCl in dioxane, followed by evaporation to dryness and ether trituration (MS: 415 [P^{+1}]).

Alternatively, lasofoxifene may be prepared using the procedures described below.

Preparation of 1-[2-[4-(6-methoxy-3,4-dihydronaphthalen-1-yl)phenoxy]ethyl]pyrrolidine: A mixture of anhydrous $CeCl_3$ (138 g, 560 mmol) and THF (500 mL) was vigorously stirred for 2 h. In a separate flask, a solution of 1-[2-(4-bromophenoxy)ethyl]pyrrolidine (100 g, 370 mmol) in THF (1000 mL) was cooled to -78°C and *n*-BuU (2.6 M in hexanes, 169 mL, 440 mmol) was slowly added over

20 min. After 15 min, the solution was added to the $CeCl_3$ slurry cooled at -78°C *via* cannula and the reaction was stirred for 2 h at -78°C. A solution of 6-methoxy-1-tetralone (65.2 g, 370 mmol) in THF (1000 mL) at -78°C was added to the arylcerium reagent *via* cannula. The reaction was allowed to warm slowly to room temperature and was stirred for a total of 16 h. The mixture was filtered through a pad of Celite™. The filtrate was concentrated *in vacuo* and 3 N HCl (500 mL) and Et_2O (500 mL) were added. After stirring for 15 min, the layers were separated. The aqueous layer was further washed with Et_2O (2x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to provide 6-methoxy-1-tetralone (22 g). The aqueous layer was basified to pH 12 with 5 N NaOH and 15% aqueous $(NH_4)_2CO_3$ (1000 mL) was added. The aqueous mixture was extracted with CH_2Cl_2 (2x). The organic solution was dried ($MgSO_4$), filtered, and concentrated to provide a brown oil. Impurities were distilled off (110°-140°C @0.2 mmHg) to yield the product (74 g, 57%).

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.27 (d, J=8.7 Hz, 2H), 6.92-6.99 (m, 3H), 6.78 (d, J=2.6 Hz, 1H), 6.65 (dd, J=8.6, 2.6 Hz, 1H), 5.92 (t, J =4.7 Hz, 1H), 4.15 (t Hz, 2H), 3.80 (s, 3H), 2.94 (t, J =6.0 Hz, 2H), 2.81 (t, J =7.6 Hz, 2H), 2.66 (m, 2H), 2.37 (m, 2H), 1.84 (m, 4H).

Preparation of 1-[2-[4,(2-bromo-6-methoxy-3,4-dihydronaphthalen-1-yl)phenoxy]ethyl]pyrrolidine: Pyridinium bromide perbromide (21.22 g, 60.55 mmol) was added portionwise to a solution of 1-{2-[4-(6-methoxy-3,4-dihydronaphthalen-1-yl)phenoxy]ethyl]pyrrolidine (23 g, 72 mmol) in THF (700 mL). The reaction was stirred for 60 h. The precipitate was filtered through a Celite pad with the aid of THF. The off-white solid was dissolved in CH_2Cl_2 and MeOH and was filtered away from the Celite. The organic solution was washed with 0.5 N aq HCl followed by saturated $NaHCO_3$ (aq). The organic solution was dried ($MgSO_4$), filtered, and concentrated to provide a brown solid (21.5 g, 83%).

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.14 (d, J=8.7 Hz, 2H), 6.97 (d, J=8.8 Hz, 2H), 6.71 (d, J=2.2 Hz, 1H), 6.55 (m, 2H), 4.17 (t, J =6.0 Hz, 2H), 3.77 (s, 3H), 2.96 m,(4H), 2.66 (m, 4 H), 1.85 (m, 4H).

Preparation of 1-{2-[4-(6-methoxy-2-phenyl-3,4-dihydronaphthalen-1 yl)phenoxy]ethyl]pyrrolidine hydrochloride (Nafoxidene hydrochloride): To a mixture of 1 [2-[4-(2-bromo-6-methoxy-3,4-dihydronaphthalen-1-yl)phenoxy]ethyl}pyrrolidine (19 g, 44 mmol), phenylboronic acid (7.0 g, 57 mmol), and

tetrakis(triphenylphosphonium) palladium (1.75 g, 1.51 mmol) in THF (300 mL) was added Na_2CO_3 (13 g, 123 mmol) in H_2O (100 mL). The reaction was heated at reflux for 18 h. The layers were separated and the organic layer was washed with H_2O followed by brine. The organic solution was dried ($MgSO_4$), filtered, and concentrated to yield 17.96 g of a brown solid. The residue was dissolved in a 1:1 mixture of CH_2Cl_2 and EtOAc (250 mL) and 1 N HCl in Et_2O (100 mL) was added. After stirring for 2 h, product was allowed to crystallize from solution and 11 g of material was collected by filtration. Concentration of the mother liquor to half its volume provided an additional 7.3 g of product.

Preparation of *cis*-1-[2-[4-(6-methoxy-2-phenyl-1,2,3,4-tetrahydro-naphthalen-1yl)phenoxy]ethyl]pyrrolidine: 1-[2-[4-(6-Methoxy-2-phenyl-3,4-dihydronaphthalen 1yl)phenoxy]ethyl]pyrrolidine hydrochloride (nafoxidene hydrochloride) (75 g, 162 mmol) was dissolved in 1000 mL of EtOH and 300 mL of MeOH. Dry $Pd(OH)_2$ on carbon was added and the mixture was hydrogenated on a Parr shaker at 50°C and 50 psi (0.34 MPa) for 68 h. The catalyst was filtered off with the aid of Celite and the solvents were removed *in vacuo*. The resulting white solid was dissolved in CH_2Cl_2 and the solution was washed with saturated $NaHCO_3$ (aq). The organic solution was dried ($MgSO_4$), filtered, and concentrated to yield an off-white solid (62.6 g, 90%).

Preparation of *cis*-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol: A mixture of *cis*-1-[2-[4-(6-methoxy-2-phenyl-1,2,3,4 tetrahydronaphthalen-1-yl)phenoxy] ethyl]pyrrolidine (12 g, 28 mmol), acetic acid (75 mL), and 48% HBr (75 mL) was heated at 100°C for 15 h. The solution was cooled and the resulting white precipitate was collected by filtration. The hydrobromide salt (9.6 g, 69%) was dissolved in $CHCl_3$/MeOH and was stirred with saturated $NaHCO_3$ (aq). The layers were separated and the aqueous layer was further extracted with $CHCl_3$/MeOH. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to yield product as an off-white foam.

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.04 (m, 3H), 6.74 (m, 2H), 6.63 (d, J =8.3 Hz, 2H), 6.50 (m, 3H), 6.28 (d, J =8.6 Hz, 2H), 4.14 (d, J=4.9 Hz, 1H), 3.94 (t, J=5.3 Hz, 2H), 3.24 (dd, J=12.5, 4.1 Hz, 1H), 2.95 (m, 4H), 4H), 2.14 (m, 1H), 1.88 (m, 4H), 1.68 (m, 1H).

The following procedures and formulations are reproduced from U.S. Patent Application No. 10/612,679, filed July 1, 2003.

The following materials may be obtained from the corresponding sources listed below:

Avicel™ PH101 (microcrystalline cellulose)	FMC Pharmaceutical (Philadelphia, PA)
Lactose Fast Flo™ 316	Foremost Corp. (Baraboo, WI)
magnesium stearate	Mallinckrodt (St. Louis, MO)
hydroxypropyl cellulose	Hercules Inc. (Hopewell, VA)
sodium croscarmellose	FMC Pharmaceutical (Philadelphia, PA)
β-cyclodextrin sulfobutyl ether	Prepared using the method described in U.S. Patent No. 6,153,746
silicon dioxide	Grace Davison (Columbia, MD)
ProSolv™ 50 (silicified microcrystalline cellulose)	Penwest, Patterson, NJ

Lasofoxifene Conventional Wet Granulation Process

(Comparative process)

The following ingredients were added to a high shear blender in the listed order.

lactose	5.000 g
microcrystalline cellulose	17.432 g
sodium croscarmellose	1.000 g
hydroxypropyl cellulose	1.250 g
silicon dioxide	0.125 g
Lasofoxifene	0.068 g

The mixture was blended for approximately 15 minutes. While blending, an appropriate amount of water (approximately 63% w/w of dry blend) was added over a 8.5 minute period and then allowed to continue blending for an additional 30 seconds to achieve the desired wet mass. The wet mass was then dried to a moisture level less than about 2% under vacuum (about 50 millibar (mB)). The dried granulation was milled through a conical mill fitted with a 0.04 inch (0.10 cm) screen and round edge impeller set at 1750 rpm speed. The mixture was blended for about 10 minutes

in a 150 cc glass bottle on a Turbula mixer. Magnesium stearate (0.125 g) was added to the mixture and then blended for about 5 minutes. The active blend was then compressed into tablets using a Kilian™ T100 tablet press (available from Kilian & Co., Inc., Horsham, PA).

Lasofoxifene Drug In Solution Wet Granulation Process
(Comparative process)

Water (100 mL) was added to a 250 mL glass beaker equipped with a mixer. While stirring, β-cyclodextrin sulfobutyl ether (0.452 g) was added followed by the lasofoxifene (0.113 g) and allowed to stir until the β-cyclodextrin sulfobutyl ether and lasofoxifene dissolved and a solution was formed. The following ingredients were then added in the order listed into a high shear blender.

lactose	5.000 g
silicified microcrystalline cellulose	17.540 g
sodium croscarmellose	1.000 g
hydroxypropyl cellulose	1.250 g

The mixture was blended for about 2 minutes. While blending, the lasofoxifene:water solution was added over a 3 minute period. The wet mass was then dried to a moisture level of less than about 1% in a 50°C forced hot air oven. The dried granulation was passed through a conical mill fitted with a 0.055 inch (0.14 cm) screen and round edge impeller set at 1750 rpm speed. Magnesium stearate (0.125 g) was added to the mixture and then blended for about 5 minutes. The active blend was then compressed into tablets using a Manesty™ F-Press tablet press (available from Thomas Engineering Inc., Hoffman Estates, IL).

<u>*Lasofoxifene Dry Granulation Process*</u>

The following ingredients were added in the order listed into a high shear blender

lactose	1052.25 g
microcrystalline cellulose	375.00 g
croscarmellose sodium	45.00 g
silicon dioxide	7.50 g
Lasofoxifene	5.25 g

The lactose, microcrystalline cellulose, croscarmellose sodium and silicon dioxide were blended for 5 minutes. The lasofoxifene was added next and blended for about 15 minutes. The active blend was then discharged from the high shear blender and blended for about 5 minutes in a twin shell "V" blender. Magnesium stearate (7.50 g) was added to the active blend and blended for about 5 minutes. The active blend was roller compacted on a Vector Freund™ roller compactor unit and milled through a rotating granulator fitted with a 0.033" (0.084 cm) screen (both available from Vector Corp., Marion, IA). The active granulation was blended for about 5 minutes in a twin shell "V" blender. Another portion of magnesium stearate (7.50 g) was added to the granulation and blended for about 5 minutes. The final blend was compressed into tablets on a Kilian™ T100 rotary press.

Immediate release low dosage formulations of the present invention were prepared as exemplified below.

1. To an appropriate sized high shear blender was added, in order: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, silicon dioxide and blended for 5 minutes at appropriate impeller and granulator speeds.

2. Lasofoxifene tartrate was introduced and blended for 15 minutes at appropriate impeller and granulator speeds.

3. Active blend was discharged from the high shear blender.

4. Active blend was charged into an appropriate size twin shell or bin blender and blended for 5 minutes.

5. One-half of the magnesium stearate was added to the active blend and blended for 5 minutes.

6. The active blend was compacted on an appropriate roller compactor unit at the appropriate roller pressure, roller speed and feed rate.

7. The active compacts were milled through an appropriate mill fitted with a 20 mesh (0.033") screen or equivalent.

8. The milled active blend was charged into an appropriate size twin shell or bin blender and blended for 5 minutes.

9. The second half of the magnesium stearate was added to the milled active blend and blended for 5 minutes.

10. The final blend was compressed on a rotary tablet press fitted with the appropriate size tooling at a weight of 100 mg.

11. Tablet cores were film coated in an appropriate size film-coating unit. The appropriate amount of opacifying and polishing film coats was applied to the tablets.

Lasofoxifene 0.25 mg Film Coated Tablet Composition:

Component	Grade	Mg/Tablet	Function
Lasofoxifene Tartrate[1]	Pfizer	0.341	Active Compound
Lactose, Anhydrous[2]	NF/USP/Eu/JP	70.159	Diluent/Filler
Microcrystalline Cellulose	NF/Eu/JP	25.000	Diluent/Filler
Croscarmellose Sodium	NF/Eu/JP	3.000	Disintegrant
Silicon Dioxide	NF/Eu	0.500	Glidant
Magnesium Stearate	NF/Eu/JP	1.000	Lubricant
Opadry II® (Y-30-13579-A)	Pfizer	4.000	
(Lactose Monohydrate)	(NF/Eu/JP)	(1.60)	Opacifying Coat
(Hydroxypropyl Methyl Cellulose 2910-15 cP)	(USP/Eu/JP)	(1.12)	(Diluent/Filler)
(Titanium Dioxide)	(USP/Eu/JP)	(0.94)	(Polymer)
(Triacetin)	(USP/Eu/JPE)	(0.32)	(Opacifier)
(FD&C Yellow No. 6 Aluminum Lake 15%-18%)	(21 CFR, E110)	(0.02)	(Plastisizer) (Colorant)
Opadry Clear® (YS-2-19114-A)	Pfizer	0.500	Polish Coat
(Hydroxypropyl Methlycellulose 2910-15cP)	(NF/Eu/JP)	(0.45)	(Polymer)
(Triacetin)	(USP/Eu/JPE)	(0.05)	(Plastisizer)
Total		**104.500**	

1. Based on a theoretical potency of 73.4%
2. Weight adjusted for slight potency changes in the lasofoxifene tartrate

Lasofoxifene 0.5 mg Film Coated Tablet Composition:

Component	Grade	Mg/Tablet	Function
Lasofoxifene Tartrate[1]	Pfizer	0.681	Active Compound
Lactose, Anhydrous[2]	NF/USP/Eu/JP	69.819	Diluent/Filler
Microcrystalline Cellulose	NF/Eu/JP	25.000	Diluent/Filler
Croscarmellose Sodium	NF/Eu/JP	3.000	Disintegrant
Silicon Dioxide	NF/Eu	0.500	Glidant
Magnesium Stearate	NF/Eu/JP	1.000	Lubricant
Opadry II® (Y-30-13579-A)	Pfizer	4.000	
(Lactose Monohydrate)	(NF/Eu/JP)	(1.60)	Opacifying Coat
(Hydroxypropyl Methyl Cellulose 2910-15 cP)	(USP/Eu/JP)	(1.12)	(Diluent/Filler)
(Titanium Dioxide)	(USP/Eu/JP)	(0.94)	(Polymer)
(Triacetin)	(USP/Eu/JPE)	(0.32)	(Opacifier)
(FD&C Yellow No. 6 Aluminum Lake 15%-18%)	(21 CFR, E110)	(0.02)	(Plastisizer) (Colorant)
Opadry Clear® (YS-2-19114-A)	Pfizer	0.500	Polish Coat
(Hydroxypropyl Methylcellulose 2910-15cP)	(NF/Eu/JP)	(0.45)	(Polymer)
(Triacetin)	(USP/Eu/JPE)	(0.05)	(Plastisizer)
Total		**104.500**	

1. Based on a theoretical potency of 73.4%
2. Weight adjusted for slight potency changes in the lasofoxifene tartrate

Claims

What is claimed is:

1. A pharmaceutical composition comprising the compound 2-methylene-19-nor-20(S)-1α,25-dihydroxyvitamin D_3 and an estrogen agonist/antagonist, or a pharmaceutically acceptable salt or prodrug thereof.

2. A composition of claim 1 wherein the estrogen agonist/antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-napthalene-2-ol or a pharmaceutically acceptable salt or prodrug thereof.

3. A composition of claim 2 wherein the (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-napthalene-2-ol is in the form of the tartrate salt.

4. A method of treating senile osteoporosis, postmenopausal osteoporosis, bone fracture, bone graft, breast cancer, prostate cancer, obesity, osteopenia, male osteoporosis, frailty, muscle damage or sarcopenia, the method comprising administering to a patient in need thereof a therapeutically effective amount of 2-methylene-19-nor-20(S)-1α,25-dihydroxyvitamin D_3 and an estrogen agonist/antagonist or a pharmaceutically acceptable salt or prodrug thereof.

5. The method of claim 4 wherein the 2-methylene-19-nor-20(S)-1α,25-dihydroxyvitamin D_3 and estrogen agonist/antagonist or a pharmaceutically acceptable salt or prodrug thereof are administered orally.

6. The method of claim 4 wherein the 2-methylene-19-nor-20(S)-1α,25-dihydroxyvitamin D_3 and estrogen agonist/antagonist or a pharmaceutically acceptable salt or prodrug thereof are administered parenterally.

7. The method of claim 4 wherein the 2-methylene-19-nor-20(S)-1α,25-dihydroxyvitamin D_3 and estrogen agonist/antagonist or a pharmaceutically acceptable salt or prodrug thereof are administered transdermally.

8. The method of claim 4 wherein the 2-methylene-19-nor-20(S)-1α,25-dihydroxyvitamin D_3 and estrogen agonist/antagonist or a pharmaceutically acceptable salt or prodrug thereof are administered substantially simultaneously.

9. The method of claim 4 wherein postmenopausal osteoporosis is treated.

10. A method of treating senile osteoporosis, postmenopausal osteoporosis, bone fracture, bone graft, breast cancer, prostate cancer, obesity, osteopenia, male osteoporosis, frailty, muscle damage or sarcopenia, the method comprising administering to a patient in need thereof a therapeutically effective amount of 2-methylene-19-nor-20(S)-1α,25-dihydroxyvitamin D_3 and (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-napthalene-2-ol or a pharmaceutically acceptable salt or prodrug thereof.

11. The method of claim 10 wherein the (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-napthalene-2-ol is in the form of the tartrate salt.

INTERNATIONAL SEARCH REPORT

IB2004/002900

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/593 A61K31/40 A61K45/06 A61P19/08 A61P19/10
A61P35/00 A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 843 928 A (RAFAL SICINSKI R ET AL) 1 December 1998 (1998-12-01) cited in the application column 4, lines 6-52 column 16, lines 23-32; claims 1,18,19	1-11
Y	WO 02/091993 A (MOSLEY RALPH TROY ; MERCK & CO INC (US); BLIZZARD TIMOTHY ALLEN (US);) 21 November 2002 (2002-11-21) page 3, lines 22-32; claims 19-27 page 15, line 15 - page 16, line 5 page 19, line 31 - page 20, line 8 page 23, line 27 - page 24, line 20 page 26, lines 26-33	1-11

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 December 2004	13/01/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Paul Soto, R

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00/61123 A (BEHRENS STEVENS MARIE LUISE ; SCHERING AG (DE); ERBEN REINHOLD (DE); K) 19 October 2000 (2000-10-19) page 2, line 30 - page 3, line 16 page 4, lines 24-37 claims 1,5,9,10	1-11
Y	US 6 486 144 B1 (MORRIS DAVID LAWSON) 26 November 2002 (2002-11-26) column 5, lines 6-35; claims 14,15	1-11
A	KOMM B S ET AL: "The ongoing saga of osteoporosis treatment" JOURNAL OF CELLULAR BIOCHEMISTRY 1998 UNITED STATES, no. SUPPL. 30/31, 1998, pages 277-283, XP001064555 ISSN: 0730-2312 the whole document	1-11
P,X	WO 2004/022068 A (WISCONSIN ALUMNI RES FOUND) 18 March 2004 (2004-03-18) page 4, lines 17-20 page 13, lines 17-19 page 15, lines 8-15 page 21; claims 10,13,25,28,38,41,51,54	1-11

INTERNATIONAL SEARCH REPORT

PCT/IB2004/002900

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 4-11
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 4-11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

IB2004/002900

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